Diagnostic Accuracy of the maximum systolic acceleration for detecting the severity of peripheral arterial disease

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Primary Objective: The Primary outcome is to evaluate the sensitivity of the ACCmax compared to the currently advised diagnostic method the ABI.Secondary ObjectivesTo evaluate the sensitivity, specificity, positive and negative likelihood ratios of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Observational non invasive

Summary

ID

NL-OMON51346

Source
ToetsingOnline

Brief title
Maximum systolic acceleration to diagnose PAD

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
intermittent claudication, peripheral arterial disease

Research involving
Human

Sponsors and support

Primary sponsor: Haaglanden Medisch Centrum
Source(s) of monetary or material Support: Bronovo Research Fonds

Intervention

Keyword: Doppler duplex ultrasound, Peripheral arterial disease

Outcome measures

Primary outcome

1.) Study parameters: ABI, TP, TBI, exercise/treadmill test, duplex ultrasonography and ACCmax calculations

2.) Primary endpoint:

a. to evaluate the sensitivity of the ACCmax compared to the currently advised diagnostic method the ABI.

Definitions of study parameters/endpoints

All definitions pertinent to PAD are based on the 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Disease, in collaboration with the European Society for Vascular Surgery (ESVS).(10)

ACCmax is a duplex-derived maximum systolic acceleration, and is calculated by computer at a single representative curve expressed in meters per second. The ACCmax is measured at the visually judged maximum derivative of the systolic phase as shown in Figure 1, and is measured distal to the stenosis.(15, 16) No additional software is necessary to obtain the ACCmax. As shown in figure 1, by clicking on two points in the screen there will be one tangent line. This tangent line must be placed manually at the maximal slope in the systolic phase at a single representative curve. The computer automatically calculates the

acceleration of the tangent line at the steepest point in m/sec2 (= maximal systolic acceleration). ACCmax should not be confused with either acceleration time (AT) or mean systolic acceleration (ACCsys), which is the slope between beginning of systolic upstroke and peak of systole and is calculated using the following equation: ACCsys = ΔVsys/AT.

Ankle-brachial Index of <0.90 is considered diagnostic for PAD, as well as a significant decrease in ABI after exercise testing (see below).

Death will be defined as death from cardiovascular causes or cerebrovascular causes and any death without another known cause. The information will be obtained from patient files, referring vascular surgeons, general practitioners or death certificates.

Duplex Ultrasonography (DUS): peripheral arterial disease is defined as >50% arterial obstruction.

Exercise/treadmill test is usually performed using the Strandness protocol at a speed of 3km/h and 10% slope. The test is stopped when the patient is unable to walk further because of pain, defining maximal walking distance. Furthermore, a post-exercise ankle SBP decrease of >30mmHg or a post-exercise ABI >20% is diagnostic of PAD.(10)

Fontaine Classification: Clinical stages of lower extremity artery disease

Toe pressure <50mmHg is considered abnormal

Toe brachial Index <0.70 is considered abnormal

Secondary outcome

To evaluate the sensitivity, specificity, positive and negative likelihood ratios of the ACCmax compared to duplex ultrasonography.

Additionally, we will also evaluate the association between the diagnosis of PAD made in the primary objective and the following secondary endpoints: all clinical and haemodynamic outcomes are assessed within 1- and 5-year postindex measurement.

a. Walking performance

b. Mortality

c. MACE

d. Progression of disease as defined by the Fontaine Classification. Measured by: ABI; TP; DUS and ACCmax

e. Revascularisation: number of procedures and time to revascularisation

f. In-stent thrombosis

Other study parameters

1. Investigate the interobserver variability (reproducibility) of ACCmax and ABI measurements

2. Investigate the correlation between the ABI and ACCmax

3. Investigate the correlation between the ABI and ACCmax in a resting state

and after treadmill testing

4. Investigate the correlation between the TP and ACCmax

5. Investigate the correlation between the ACCmax and duplex ultrasound in

patients with and without DM, and compare the results to ABI and TP.

Study description

Background summary

Epidemiology
Peripheral arterial disease (PAD) is a common vascular disease with a preference for the lower extremities, and is estimated to affect 200 million people worldwide, with the burden of disease presenting in the elderly population.(1) PAD is caused by atherosclerosis, and progresses due to increased arterial plaque formation and thus reduction in blood flow and oxygen supply to the extremities. Reduced oxygen supply in the extremities leads to symptoms such as ischemic pain, and the development and impaired healing of ulcers. Risk factors for PAD include age, gender, ethnicity, smoking and Diabetes Mellitus (DM).(2)

It is estimated that the population of persons 65 years old and over will increase 44% in the coming 20 years. The prevalence of PAD in the general population in the Netherlands is an estimated 7% to 56% in patients over 55 and 85 years old, respectively. For the larger The Hague area, this PAD prevalence may be an underestimation as the population is of lower socio-economic status (SES) and of larger multinational background including a large Surinam-Hindustan community with a high-risk cardiovascular profile including high rates of DM.

PAD can be divided into four stages according to the Fontaine classification system, see Table 1.(3) Fontaine II includes patients with intermittent claudication, and has a 5-year overall and vascular mortality rate of 9% and 3%, respectively.(4, 5) One-fifth of Fontaine II patients experience worsening symptoms, and in some eventual amputation. Furthermore, Fontaine II is often the index presenting symptom in patients with underlying cardiovascular disease, with 21% of Fontaine II patients developing other cardiovascular events in the course of five years.(5) While these numbers warrant extensive secondary prevention and surveillance in PAD patients, current guidelines are based on either recent small studies or dated larger American studies that may no longer be relevant due to changing diagnostic and treatment strategies.(6) There is thus a need for large contemporary studies on the epidemiology and

natural progression of Fontaine II patients.

Table 1: Fontaine Classification

FONTAINE CLASSIFICATION	
STAGE	Symptoms
I	Asymptomatic
II	IIa Non-disabling intermittent claudication
	IIb Disabling intermittent claudication
III	Ischaemic rest pain
IV	Ulceration or gangrene

Diagnostics of Fontaine II PAD

A broadly accepted diagnostic modality is the ankle-brachial index (ABI). This is a measurement of systolic blood pressure differences between the arm and ankle, where an ABI of less than 0.9 is interpreted as a sign of significant arterial stenosis.(3) Other non-invasive techniques include exercise testing, a means of precipitating ischemic symptoms, toe pressure (TP), and the toe-brachial index (TBI). The TP and TBI measurement are taken distally in the hallux of the foot, and are said to be less influenced by the presence of medial sclerosis. However, both TBI and TP can provide falsely elevated values as a result of incompressible digital arteries. The literature, however, is not unanimous on the accuracy of this method.(7) Methods focusing principally on microcirculation include tissue oximetry (TcPO2). This method shows varied potential in the research setting due to limited repeatability.(8) More invasive techniques include computed tomography angiography (CT-A)and magnetic resonance angiography (MR-A). While these methods are effective in assisting the decision-making process regarding targets for revascularization, they are of limited value in assessing tissue perfusion in instances of collateral formation or microvascular occlusion.(9) Digital subtraction angiography (DSA) was previously considered as a standard vascular imaging technique. However, due to the invasive nature of this technique it is infrequently applied in the preclinical setting, with the exception of instances of discrepancy between non-invasive techniques.(10)

Of the above-mentioned diagnostic modalities, the ABI is the most frequently adopted technique for initial PAD diagnosis in a primary care setting. However, ABI measurements can be unreliable through incompressible arteries as a result of medial calcific sclerosis that occur primarily in patients with DM, advanced age, or end-stage renal disease. It is expected that one in every three Dutch persons over 45-years of age will develop DM, and the current prevalence of PAD in people with diabetes is 20-30%.(11) With an increasing burden of disease timely diagnosis of PAD in this patient group is paramount, however two recent reviews have shown poor results and insufficient evidence for the standard test

for diagnosing PAD among patients with DM.(12, 13)

New imaging techniques are therefore required to improve early detection and assist in appropriate and timely management of symptomatic disease and its* complications. A novel Doppler ultrasonography (DUS) parameter, the maximum systolic acceleration (ACCmax), is being investigated as an alternative modality to diagnose PAD. The ACCmax measures the acceleration of blood flow by quantifying the maximal steepness of the systolic doppler curve. This technique is believed to provide more accurate measurements across all patients, including those with incompressible arteries such as diabetes mellitus patients, and can provide more insight into the anatomical location of a possible atherosclerotic stenosis.(14, 15) This technique offers a promising alternative to the ABI, TP or TBI and has recently gained popularity among our affiliated and other hospitals.(14, 16) However, while promising and easily applicable, the use of ACCmax still needs large-scale validation in the general PAD II population, with specific research focussed on the application of this technique in a pre-clinical setting.

Hypothesis and Rationale
It is hypothesized that validation of the ACCmax will result in the implementation of a non-invasive PAD diagnostic tool with improved sensitivity and specificity in comparison to current methods, namely duplex ultrasonography and the ankle-brachial index.

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Study objective

Primary Objective:
The Primary outcome is to evaluate the sensitivity of the ACCmax compared to the currently advised diagnostic method the ABI.

Secondary Objectives
To evaluate the sensitivity, specificity, positive and negative likelihood ratios of the ACCmax compared to duplex ultrasonography.
Additionally, we will also evaluate the association between the diagnosis of PAD made in the primary objective and the following secondary endpoints: all clinical and haemodynamic outcomes are assessed within 1- and 5-year postindex measurement.
a. Walking performance
b. Mortality
c. MACE
d. Progression of disease as defined by the Fontaine Classification
e. Revascularisation: number of procedures and time to revascularisation

f. In-stent thrombosis

Other study objectives
1. Investigate the interobserver variability (reproducibility) of ACCmax and ABI measurements
2. Investigate the correlation between the ABI and ACCmax
3. Investigate the correlation between the ABI and ACCmax in a resting state and after treadmill testing
4. Investigate the correlation between the TP and ACCmax
5. Investigate the correlation between the ACCmax and duplex ultrasound in patients with and without DM, and compare the results to ABI and TP.

Study design

This is a prospective observational diagnostic study.
This study will be performed in The Hague, the Netherlands and include patients receiving care in MijnKliniek and the Haaglanden Medical Centre Hospital (HMC) in this region.

The diagnostic value of the ACCmax will be analysed in an observational setting.
Vascular laboratory assistant A. The laboratory assistant will begin with the ACCmax measurement. The ACCmax value will be recorded after which the index tests will be performed. In this way the ACCmax result will be blinded.
Thereafter the following diagnostic tests will be performed: duplex ultrasound of all arteries from the aorta to the lower limb, ABI, TP, TBI, treadmill exercise testing.
Vascular laboratory assistant B. The ACCmax will be measured at the distal tibialis posterior artery, dorsalis pedis artery in the context of the interobserver variability measurement.

The prognostic value of the ACCmax will be evaluated in terms of secondary endpoints, clinical outcomes. A standard follow-up period of 1- and 5 years with a physical consultation at 4 months and telephone consultation at 1- and 5 years will be set. Should a treatment intervention fail, or a patient return at an earlier interval due to progression of disease this will be noted.

Study burden and risks

There are no risks for patients associated with participation in this study. Participation in this study will require an extra 45 minutes consultation time during the primary consultation in order to perform an extra ACCmax measurement. Furthermore, at a regular follow-up visit at 4 months a second ACCmax measurement will be performed. The patient will be required to fill out

a questionnaire three times during the study period.

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

18 years of age and older

Exclusion criteria

Unable to give informed consent or have a life expectancy of less than one year due to a non-cardiovascular risk profile.

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-03-2023
Enrollment:	273
Type:	Actual

Ethics review

Approved WMO

Date:	24-10-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL79711.058.22