Maximal systolic acceleration in atherosclerotic vascular disease

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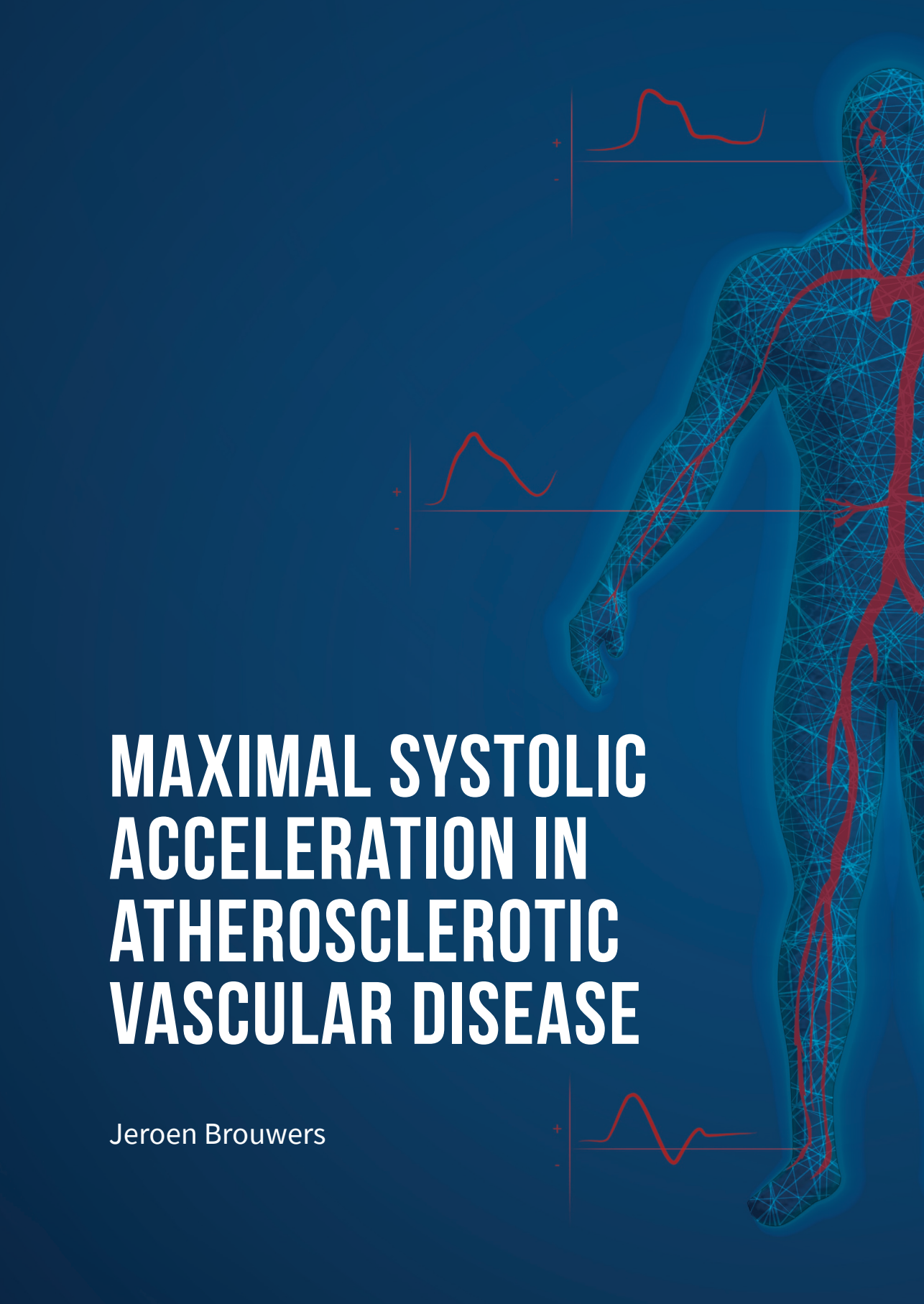

MAXIMAL SYSTOLIC ACCELERATION IN ATHEROSCLEROTIC VASCULAR DISEASE

Jeroen Brouwers

Maximal Systolic Acceleration in atherosclerotic vascular disease

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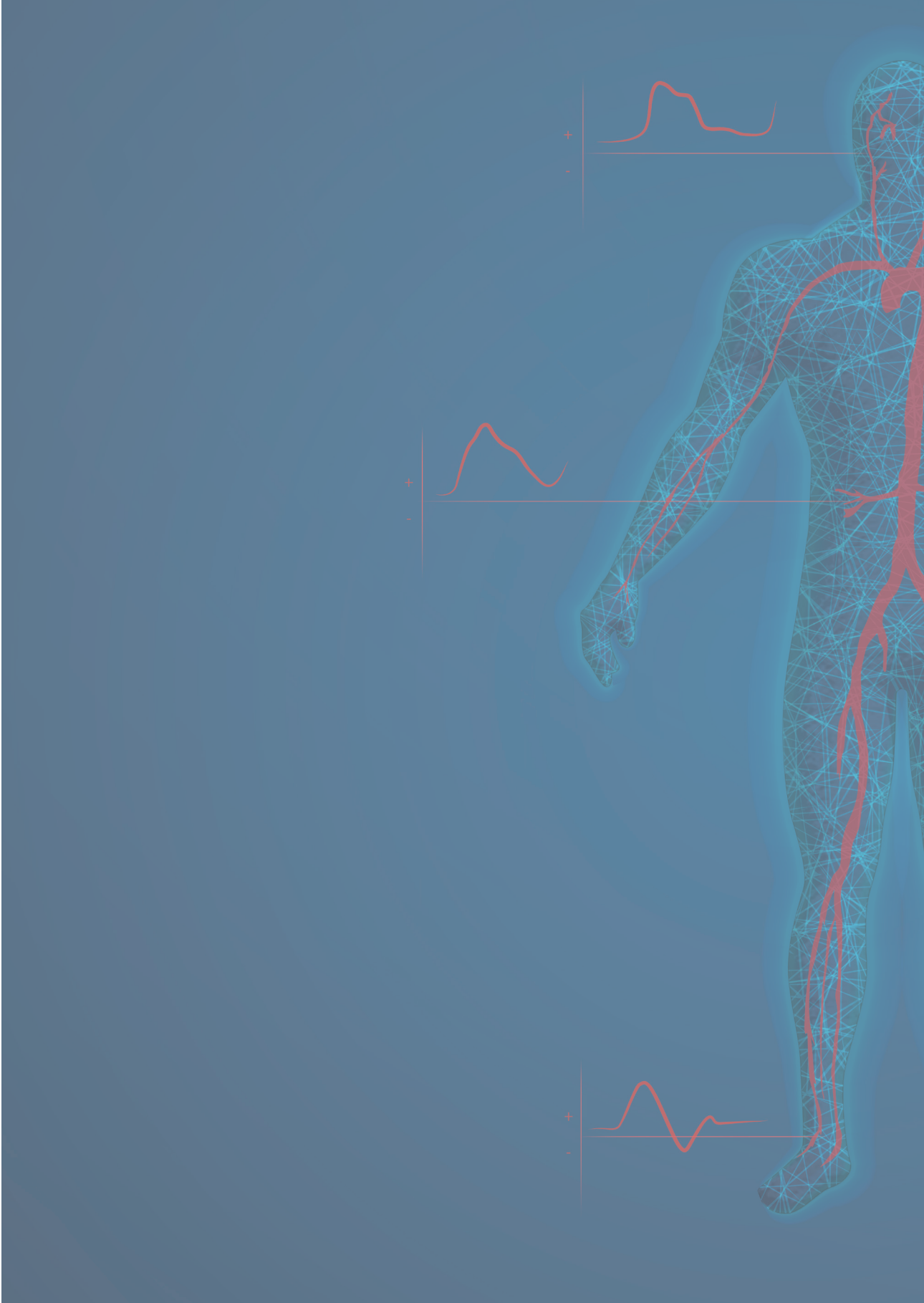
Chapter 1

Introduction and outline of this thesis



1.1 General features in atherosclerosis

Introduction

In 1575 for the first time, aspects of atherosclerosis were described by Follopius, however there are indications that this disease is much older. In several autopsy studies of mummies – from probably more than 5000 years ago – plaque like lesions were discovered with similar features to the atherosclerotic lesions of today.[1-3] The term atheroma was first used by Albert von Haller in 1755. He injured his finger on a calcification of the abdominal aorta during autopsy.[3,4] In the fifties of the 19th century Virchow presented the 'inflammatory theory' and described processes from injury to the artery wall, with an association of inflammatory and proliferative responses, resulting in atherosclerotic lesions.[5,6] In 1999 Ross published a landmark paper in the New England Journal of Medicine and emphasized the inflammatory process of atherosclerotic disease. He also described atherosclerosis did not result only from lipid accumulation,[7] thereafter it was widely accepted that atherosclerosis is a complex inflammatory driven process.

Composing an atheromatous plaque is a time-consuming process and takes several years to develop. It is a complex sequence of cellular events of the arterial wall and local vascular circulating factors. Endothelial dysfunction is an early process in the development of atherosclerosis. There is a disruption in the endothelial barrier permeability that is part of inflammatory response. Our innate and adaptive immune systems are involved in the progression of atherosclerosis. As a result of the formatted plaque the lumen of the artery is narrowed.[8-10]

Nowadays atherosclerotic related cardiovascular disease is a massive public health problem and is the most common cause of death in all regions in the World (excluding sub-Saharan of Africa).[10,11] In the Netherlands 1,5 million people suffer from chronic cardiovascular disease.[12] It is well known that atherosclerotic disease increases with increased prosperity. Several risk factors are recognized and include smoking, diabetes mellitus (DM), obesity, family history, unhealthy diet, elevated cholesterol levels and high blood pressure. Prevention of developing atherosclerotic related problems can be achieved by countermeasure these risk factors. Furthermore, cardiovascular risk management (CVRM) is an important strategy to reduce atherosclerotic related problems.[5,13,14]

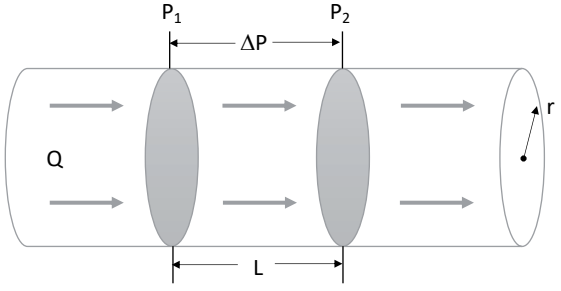
Although atherosclerosis is a generalized disease, it has several preferred locations to develop: carotid bifurcation, aortic arch branches, coronary arteries, aortic bifurcation, iliac vessels, femoral bifurcation, superficial femoral artery and lower leg vessels. Due to the different locations of an atherosclerotic plaque, there are multiple clinical manifestations

related to atherosclerosis, from cerebral ischemic attacks as a result of a carotid artery stenosis, to complaints of claudication intermittent due to peripheral arterial disease (PAD) of the lower extremity. Hence, in vascular surgery a distinction can be made in atherosclerosis arterial disease based on the location of the plaque.

Arterial Hemodynamics

An arterial stenosis caused by atherosclerotic plaque is the primary physiologic abnormality in arterial disease and leads to insufficient tissue perfusion and oxygen delivery. The impact of the stenosis is related to the degree of stenosis and causes increased energy losses in the arterial flow. The following aspects contribute to this process.

According to Poiseuille's law (figure 1), as a result of the stenotic segment the energy losses are inversely proportional to the fourth power of the radius at the stenosis. Moreover, the energy losses are directly proportional to the length of the stenosis. Hence, the degree of the stenosis (radius of the stenotic segment) has much more impact on the energy impairment of the flow than the length of the stenotic segment.[15]



$$Q = \frac{\Delta P \, r^4 \, \pi}{\eta \, L \, 8}$$

Figure 1: Poiseuille's law for a circular lumen
ΔP is pressure drop, η is the coefficient of viscosity, L is the length of the lumen, Q is the volume flow (cm^3/sec), and r is the radius of the lumen

Furthermore, energy losses in the arterial system also occur as a result of the entrance and the exit from a stenosis, and is responsible for a large portion of the resistance. This energy loss depends on the shape of the entrance and exit. An abrupt change at the entrance of a stenosis results in more energy losses compared to a gradual tapering of the lumen. In the exit area of a stenosis there is a kinetic energy excess due to turbulent flow directly distal from the stenosis. As a result of these energy losses, two identical separate stenosis

in series have more impact on the energy losses in the arterial system than one stenosis with a length of the two stenosis together with the same degree of stenosis.[15]

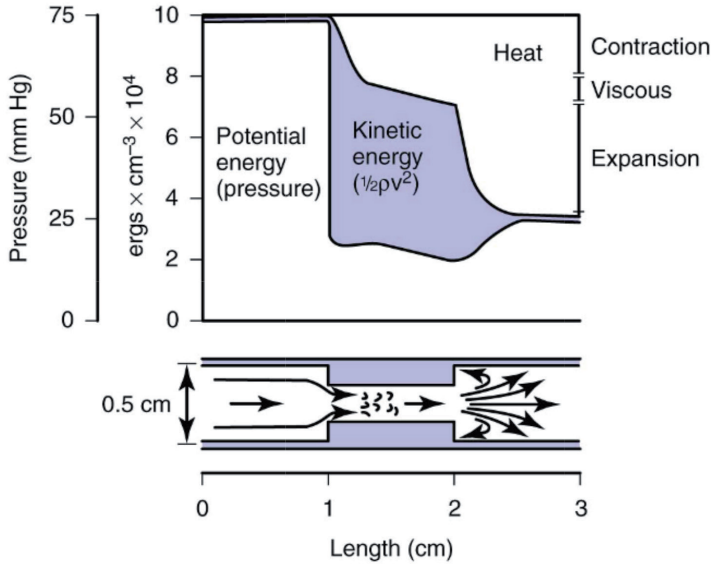


Figure 2: energy losses through a stenosis
In this figure the energy losses by blood are shown for a 1 cm long stenosis. Flow is assumed to be unidirectional and steady
This figure was published in Rutherford's Vascular Surgery 2014, Cronenwett et al. chapter: Arterial Physiology, page 137, Copyright Elsevier.

In **chapter 3** these arterial hemodynamic principles are implemented in a modified arterial stenosis model to investigate a new hemodynamic parameter, maximal systolic acceleration (ACCmax), described later in this introduction.

In a completely concentric stenosis, the reduction in lumen diameter can be directly translated to the reduction in cross-sectional area; for example, a 50% reduction in the lumen diameter translates to a 75% reduction in cross-sectional area (as shown in figure 3).[16] Therefore, it is of the utmost importance, when describing a stenosis, to realize the differences between diameter and cross-sectional area reduction. It may be crucial in decision making regarding intervention, particularly in carotid artery disease. Therefore, this phenomenon should be taken into account when discussing and describing luminal stenosis in arterial diseases. However, this mathematical feature cannot be extrapolated blindly for most atherosclerotic plaques as they tend to be asymmetrical.

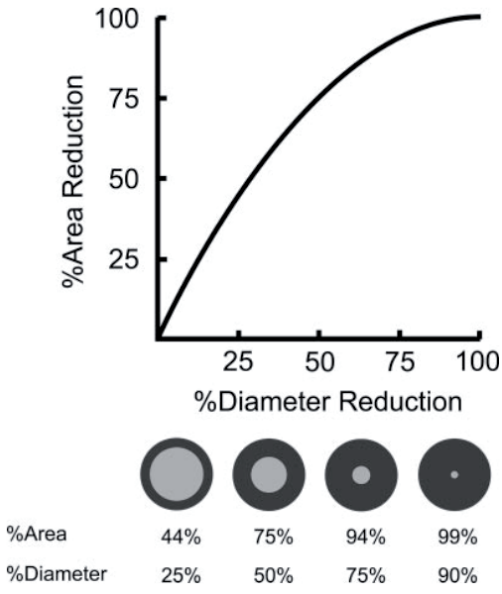


Figure 3: Relation between diameter and cross-sectional area reduction
The relationship is shown between diameter and cross-sectional area reduction in a completely concentric stenosis. The following equation is used A = D X (2-(D/100)
A = percentage of area reduction
D = percentage of diameter reduction.
This figure was published in RadioGraphics 2005. Ota et al. Quantitative Vascular Measurements in Arterial Occlusive Disease; 25:1141-1158. Copyright Radiological Society of North America.

Doppler ultrasonography (DUS) general features

In this thesis, the focus will be on non-invasive diagnostics in several atherosclerotic vascular diseases. Particularly Doppler ultrasonography (DUS) parameters will be discussed. Ultrasound use sound waves with frequencies >20 000 cycles per second (Hz), these are not audible for the human ear. This technology combines B-mode, color Doppler imaging (anatomic) information and pulsed Doppler spectral analysis (acquisition of blood flow). DUS converts electrical activity to mechanical energy (ultrasound) and vice versa. So, the device can transmit and receive ultrasound signals and make images of tissue anatomy and characterize blood flow. By using B-mode ("brightness") technology it is possible to get real-time gray-scale imaging. Two types of DUS displays are possible. Firstly, color-flow Doppler image used a color-encoded map superimposed on the gray-scale B-mode to show flow velocity. Secondly, the spectral Doppler refers to ultrasound modalities which show graphical representations of flow velocity over time.[17,18]

Several pulsed Doppler spectral parameters are used for test interpretation: peak systolic velocity (PSV), PSV ratio, end-diastolic velocity (EDV), resistive index (RI) and acceleration time (AT), also shown in figure 4 and discussed in the following chapters.

Maximal systolic acceleration (ACCmax)

This thesis will focus on the new velocimetric doppler-derived parameter, maximal systolic acceleration (ACCmax). Bardelli et al. described the ACCmax in 2006 for detection of renal

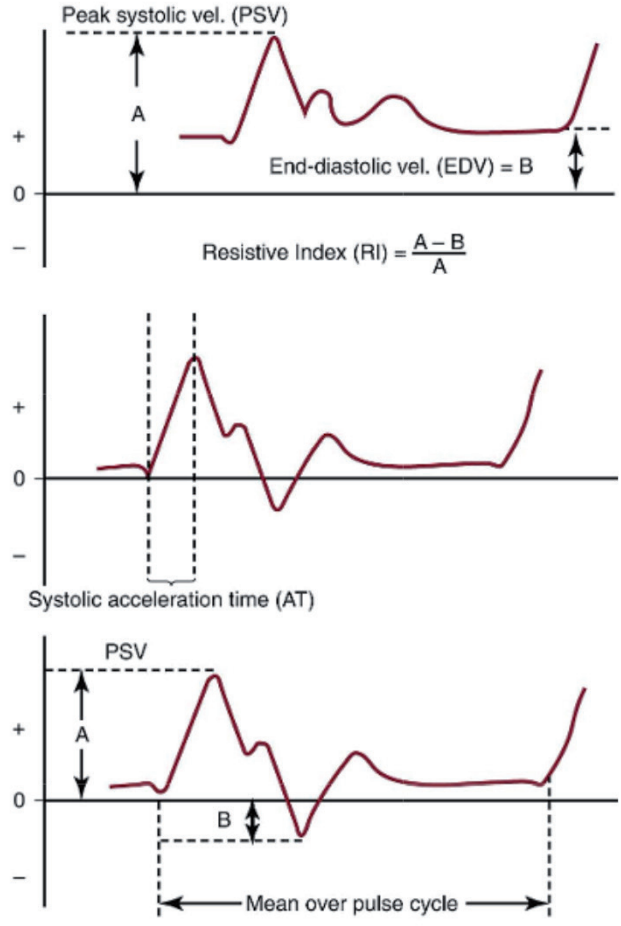


Figure 4: Doppler spectrum
Several Doppler spectral parameters are shown.
PSV = peak systolic velocity, EDV = end-diastolic velocity, RI = resistive index, and AT acceleration time.
This figure was published in Rutherford's Vascular Surgery 2014, Cronenwett et al. chapter: A Vascular Laboratory, page 234, Copyright Elsevier.

artery stenosis.[19] Subsequently a couple of clinical studies were published about the ACCmax in renal artery stenosis[20,21] and as a bedside test in PAD of the lower extremity.[22,23]

The ACCmax is calculated by a computer at a single representative curve and occurs at the maximal slope in the systolic phase (expressed in m/sec^2). Figure 5 shows an example of a normal and a divergent waveform including the ACCmax. It is important to note that the ACCmax occurs at the maximal slope in the systolic phase. No additional software is necessary to obtain the ACCmax. 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. The computer automatically calculates the acceleration of the tangent line in m/sec^2 (= maximal systolic acceleration). The ACCmax is always measured distal to the stenosis (for example at the distal posterior tibial artery). ACCmax should not be confused with 'mean systolic acceleration' (ACCsys), which is slope between beginning of systolic upstroke and peak of systole and is calculated using the following equation: ACCsys = ΔVsys/AT.

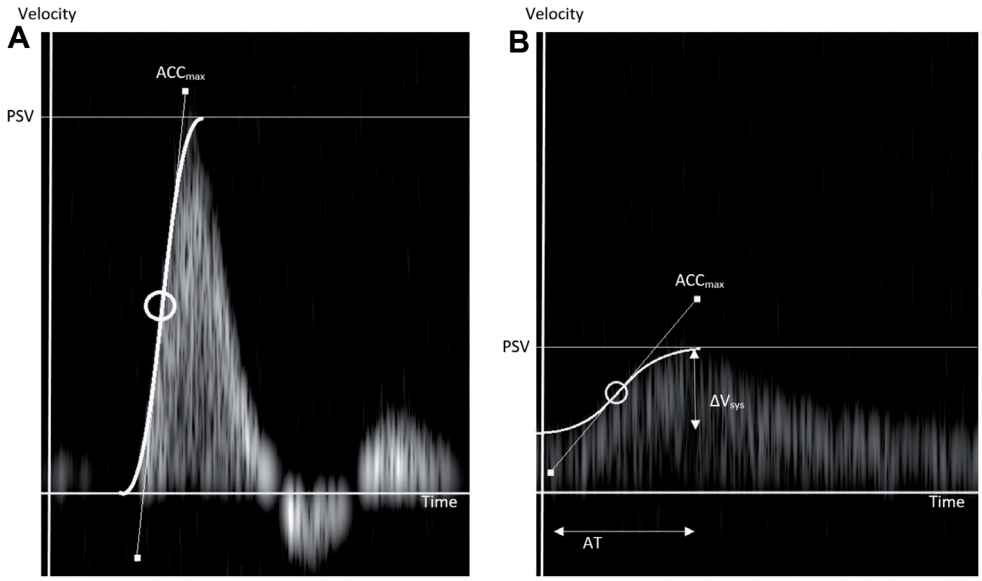


Figure 5: Example analysis of Doppler spectrum.
A, Normal triphasic Doppler waveform. Maximal systolic acceleration (ACCmax) is measured at inflection point at which upstroke changes from concave up to concave down. It is equal to slope of tangent line on curve at inflection point. B, Example of abnormal monophasic Doppler wave- form. ACCmax, peak systolic velocity (PSV), acceleration time (AT), and systolic velocity gradient (ΔVsys) are shown. ACCmax is measured at visually judged maximum derivative of systolic phase.
This figure was published in J Vasc Surg 2020. Brouwers JJWM et al. Using maximal systolic acceleration to diagnose and assess the severity of peripheral artery disease in a flow model study; 71(1):242-249. Copyright Elsevier.

In various atherosclerotic arterial diseases, conventional DUS parameters (e.g., PSV and PSV ratio) have a different role. In carotid artery disease, DUS parameters are part of the screening method. In contrast, in PAD of the lower extremity these DUS parameters are useful in the work-up to an intervention, and not part of the primary diagnostics. Several non-invasive diagnostics will be discussed per vascular disease in the following chapters. In this thesis, the ACCmax will only be used as screening method/bedside test for different atherosclerotic diseases. So, the conventional DUS parameters regarding PAD of the lower extremity remain out of scope in this thesis.

1.2 Atherosclerotic vascular diseases

In the present thesis, the following atherosclerosis arterial diseases are discussed: PAD of the lower extremity, carotid artery stenosis and renal artery stenosis**.**

Peripheral arterial disease (PAD) of the lower extremity

Peripheral arterial disease (PAD) of the lower extremity is considered a clinical manifestation of systemic atherosclerosis. It is estimated that approximately 202 million people are suffering from PAD worldwide.[24] In the United States the estimated prevalence PAD is approximately 10 percent of people older than 55 years.[25] Only half of the people are considered symptomatic of lower extremity PAD when using only ABI to diagnose PAD.[26] However, it is important to identify patients with PAD because these patients have a high rate of morbidity and mortality from myocardial infarction and stroke. Therefore, prompt cardiovascular risk management is indicated.[17]

Medial arterial calcification (MAC)

Medial arterial calcification (MAC) is characterized by calcific deposits within the media of the arterial wall, also described as Mönckeberg's arteriosclerosis. MAC on its own does not cause an intraluminal stenosis. MAC is typically diffuse and circumferential. It leads to arterial stiffness causing incompressible arteries, which hamper non-invasive pressure measurements.[27] MAC can occur in patients with chronic kidney disease (CKD)[28,29] and in approximately one third of the patients with DM, particular in patients with neuropathy.[30] Furthermore, MAC is detected in up to 70% of the amputations for critical limb ischemia.[31,32]

Of all patients with PAD in the U.S. approximately 20-30% also suffer from DM.[33] Vice versa, patients with DM have a fourfold higher risk of developing PAD compared to patients without DM.[34] The prevalence of PAD in people with DM is 20-30%[33], and increases to 65% in patients with diabetic foot ulcer (DFU).[35] Moreover, it is expected that the number of patients who have DM will increase to nearly 370 million people by 2030 worldwide. One out of 4 patients with DM will develop a DFU during their lifetime.[36] In these patients PAD

is a strong predictor of nonhealing foot ulcers.[30] Therefore, all patients with DFU must be screened for PAD.[37,38]

Diagnostics

Several non-invasive tools are currently used for diagnosing and assessing the severity of atherosclerotic PAD of the lower extremity. In the text below the most frequently used diagnostics will be mentioned.

ABI is the first-line non-invasive tool for screening and diagnosis PAD. An ABI <0.90 diagnoses lower extremity PAD (>50% stenosis) with a sensitivity 75% and specificity of 86%.[39] However, in patients with MAC (i.e., DM, CKD or CLI) the ABI can be misleading due to incompressible arteries. An ABI >1.3 is characteristic for MAC[40], however MAC may also be present in patients with an ABI <1.3, leading to false normal ABI. Both TBI and TP are generally considered to be more reliable indicators of PAD severity in patients with incompressible crural and/or pedal arteries.[41] In patients with ABI >1.30, TP and TBI can be used. However, both TBI and TP can also provide falsely elevated values as a result of incompressible digital arteries.[42,43] Other bedside tests to diagnose PAD–such as Transcutaneous oxygen pressure (TcPO2) and continuous wave Doppler (CWD) analysis–will be discussed in the next chapter.

Is there a problem?

In general, the literature is sparse and of insufficient quality to judge the bedside tests in patients with DM.[44,45] However, the bedside diagnostics should be tested in a wider context, instead of only in patients with DM. MAC causes incompressible arteries and is the underlying problem of the poor performance of the bedside tests. Thus, bedside tests must not only investigate in patients with DM, but in all patients prone to MAC such as patients with CKD and ABI >1.3. There is a lack of a complete overview of diagnostic performance of bedside tests in patients with MAC. To the best of our knowledge, we performed the first systematic review about bedside tests to diagnose PAD in patients prone to MAC (**Chapter 2**).

Furthermore, two recent reviews[44,45] showed the poor results and insufficient evidence of currently used bedside tests for diagnosing PAD among patients with DM. These authors advocated for more studies and an alternative diagnostic technique. **Chapter 3** and **4** show fundamental results of the new diagnostic parameter *ACCmax* in arteriosclerotic disease. In contrast to external blood pressure measurements (ABI, TBI and TP), during ACCmax measurements there is no external blood pressure measurement that can be influenced by vessel stiffness. Therefore, ACCmax has potential benefits, particular in patients with MAC.

Carotid artery stenosis

Every year 1.4 million strokes occur in the European population of 715 million people.[46] It is the second most common cause of death and as such a substantial financial burden to Europe; the costs exceed 38 billion Euros per year.[47] Approximately 87% of the strokes in the United States have an ischemic etiology.[48] An atherosclerotic carotid artery stenosis accounts for 10-12% of all ischemic strokes. Mostly the carotid bifurcation and the origin of the internal carotid artery (ICA) is affected by atherosclerosis.[49,50] In this segment low wall shear stress is occur, resulting in flow stagnation and appears to be at increased risk for development of atherosclerotic plaque.[51]

Symptomatic carotid disease is defined as neurologic symptoms that are sudden in onset and referable to the associated ICA distribution; ipsilateral to the stenosis. Neurologic symptoms consist of a transient ischemic attack (TIA), or an ischemic stroke.[52] About 10-15% of all patients suffering from a stroke will experience a new thromboembolism event when an ICA stenosis >50% is present.[53]

Large long-term trials with respect to the quantification, treatment, and outcome of carotid artery stenosis are the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST).[54,55] Using pooled data from these trials and reassessing the data obtained using the NASCET method, carotid endarterectomy (CEA) was found to be beneficial in neurologically symptomatic patients with an ICA diameter reduction of ≥50% on digital subtraction angiography (DSA), excluding patients with a near-occlusion.[56]

Doppler ultrasonography (DUS) is the primary evaluation of ICA stenosis and treatment determination.[57,58] DUS is a fast, non-invasive, safe and relatively inexpensive technique. It combines velocimetric measurements of the blood flow with gray-scale B-mode imaging of the vessels, thereby providing the degree of stenosis which is one of the key variables for clinical decision-making.[59] Although in many centers additional imaging (computed tomographic angiography (CTA) or MR angiography (MRA)) is obtained when intervention is considered, in some regions a majority of surgical interventions of the carotid artery is based on DUS-imaging alone.[60] Moreover, the European and American guidelines mention the option of DUS alone to make a decision regarding intervention.[57,58] Therefore, the accuracy of this imaging technique is of the utmost importance.

In a Consensus Conference of the Society of Radiologists in Ultrasound DUS-imaging was evaluated for carotid artery stenosis. Consensus was made that DUS-imaging relies on four parameters: peak systolic velocity (PSV) in the ICA, optical estimation of the stenosis, PSV ratio (PSV ICA/PSV common carotid artery (CCA)), and the end diastolic velocity (EDV) in the ICA.[59] Table 1 gives an overview of these DUS parameters including the different thresholds.

Notice that all four parameters are measured at the level of the stenosis and can therefore be influenced by local distorting factors. Presence of calcified atherosclerotic plaques and near occlusions can hamper these four measurements, and may lead to inaccurate results.[61-64] The ACCmax is measured distal to the stenosis and avoids influences of these local distorting factors. Therefore, ACCmax could be an interesting additional feature in determining the degree of ICA stenosis. In **chapter 5** the first results of ACCmax in patients with ICA stenosis are presented.

	Primary parameters		**Additional parameters**	
Degree of stenosis (%)	ICA PSV (cm/sec)	Plaque estimate (%)*	ICA/CCA PSV ratio	ICA EDC (cm/sec)
Normal	<125	None	<2.0	<40
<50	<125	<50	<2.0	<40
50-69	125-230	≥50	2.0-4.0	40-100
≥70 (but less than near occlusion)	>230	≥50	>4.0	>100
Near occlusion	High, low, or undetectable	Visible	Variable	Variable
Total occlusion	Undetectable	Visible, no detectable lumen	Not applicable	Not applicable

Table 1: DUS criteria for diagnosing ICA stenosis[59]
ICA = internal carotid artery, CCA = common carotid artery, PSV = peak systolic velocity, EDV = end diastolic velocity
*Plaque estimate (diameter reduction) with gray-scale and color Doppler ultrasonography

As mentioned before and showed in figure 3 it is important to realize the differences between diameter and cross-sectional area reduction. However, there is currently no consensus to what extent measurement of cross sectional area reduction differs from measurement of diameter reduction in a clinical setting. Previous mentioned landmark trials (NASCET and ECST)[54,55] determined thresholds based on diameter reduction. In daily clinical practice it is noticed, some radiologists measure cross sectional area reduction to determine the degree of ICA stenosis, but it is unclear to what extent this occurs. To address this question, we generated a questionnaire for radiologists. The results are shown in **Chapter 6**, furthermore the interpretations and consequences of these specific measurements are also discussed to in detail.

Renal artery stenosis

The primary cause of renal artery stenosis (RAS) is atherosclerosis (90%), followed by fibromuscular dysplasia (FMD), particular seen in young (female) adults.[65-67] RAS is a common cause of secondary hypertension and ischemic renal failure.[65] It may be present in 5-10% of the overall population and increased in high-risk populations and advancing

age.[66] There is an association with male gender, hypertension, smoking, DM, CKD, aorto-iliac occlusive disease and coronary artery disease.[65]

DUS is used as first-line imaging to detect RAS. PSV in the main renal artery is the most frequently used DUS measurement.[39] Alternative, the ACCmax can be used to detect RAS with a sensitivity of 83–94%, note that ACCmax is measured distal to the stenosis in the interlobar artery (intrarenal).[19-21] Another intrarenal DUS parameter is the resistive index (RI). The RI is modified by vascular resistance and vascular compliance.[68] Increased RI is correlated with arteriolosclerosis, glomerulosclerosis and tubulointerstitial damage.[69] Moreover, a high RI correlates with no improvement in renal function and blood pressure after renal revascularization.[70-72] However, there is no consensus which patients will benefit from revascularization.

All patients suffering from symptomatic RAS should receive medical treatment.[66] However, which patient should undergo therapeutic revascularization is far more controversial. Routine revascularization is not recommended in RAS.[39] In the landmark trials (ASTRAL, STAR and CORAL)[73-75] no significance difference in blood pressure, renal function and cardiovascular events were found between revascularization plus medical therapy and medical therapy alone. As a result of criticism[76-78] concerning the design of these trials and various observational studies [79-81] showing beneficial outcome of renal artery revascularization in selected patients, there could be a subgroup of patients who will benefit from revascularization. In **chapter 7** the selection of this subgroup is discussed, using our non-invasive prediction model.

1.3 Outline of this thesis

The aim of this thesis is to establish the primary validation of the maximal systolic acceleration (ACCmax) in atherosclerotic vascular disease.

Part I Peripheral arterial disease of the lower extremity

In **chapter 2** the current used bedside tests to diagnose PAD were evaluated in a systematic review for patients prone for medial arterial calcification (MAC). Since external pressure measurements (ABI/TBI) can lead to false high/normal results, we investigated a new Doppler-derived measurement ACCmax to detect an arterial stenosis. In **chapter 3** a flow model study was performed to investigate the correlation between the ACCmax and the intra-arterial pressure gradient for different degrees of stenosis. In **chapter 4** the next step is presented, the ACCmax was investigated in an in vivo study where an arterial stenosis was mimicked by compression on the common femoral artery in healthy individuals. The currently used bedside tests were compared to the ACCmax in this experimental setting.

Part II Carotid artery stenosis

In **chapter 5** a retrospective study is presented to show the first results of ACCmax in detecting ICA stenosis. Furthermore, the ACCmax was compared to the ICA PSV and PSV ratio (PSV ICA/PSV CCA) to detect a 50% and 70% ICA stenosis. **Chapter 6** investigates which method (reduction in diameter or area) radiologists typically use to assess the degree of ICA stenosis on CTA.

Part III Renal artery stenosis

Current literature shows there might be patients who will benefit from an intervention if a symptomatic renal artery stenosis is present. **Chapter 7** shows a study to identify non-invasive prognostic parameters (ACCmax and RI) that can select these patients who will have a positive response from renal revascularization.

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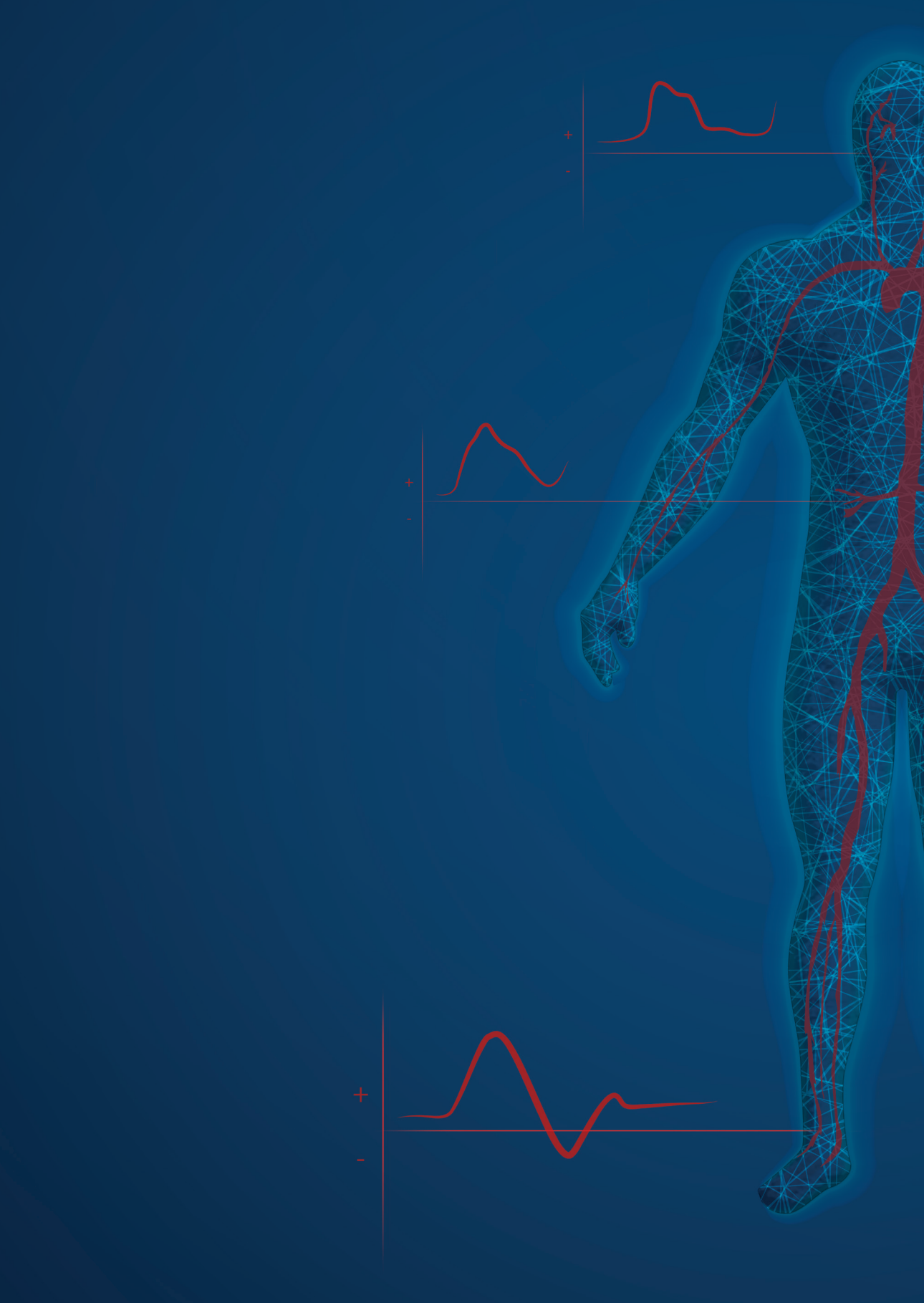
Part I

Peripheral arterial disease of the lower extremity



Chapter 2

Reliability of bedside tests for diagnosing peripheral arterial disease in patients prone to medial arterial calcification: a systematic review

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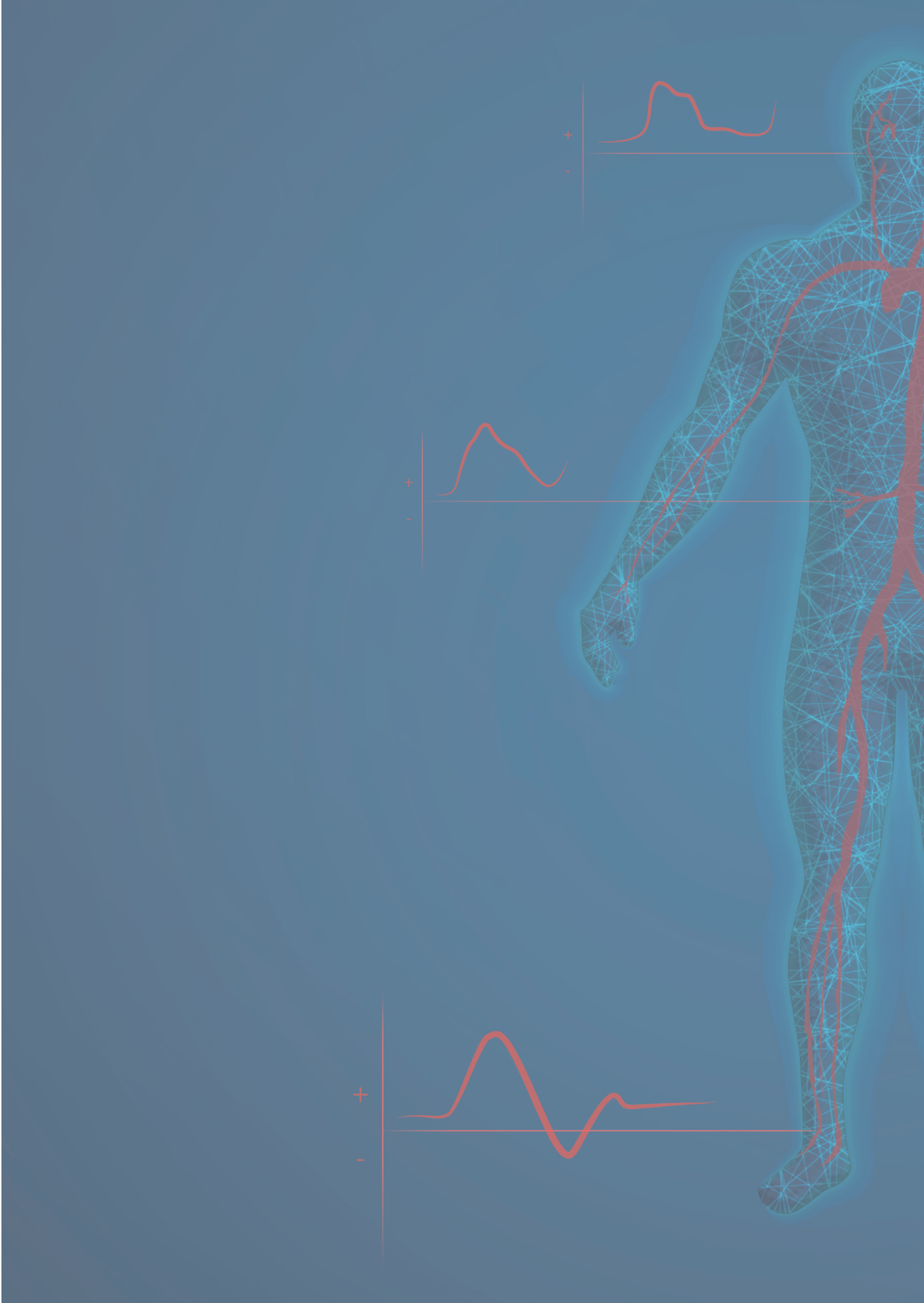

Background

Medial arterial calcification (MAC), frequently associated with diabetes mellitus (DM) and chronic kidney disease (CKD), is a systemic vascular disorder leading to stiffness and incompressible arteries. These changes impede the accuracy of bedside tests to diagnose peripheral arterial disease (PAD). This review aimed to evaluate the reliability of bedside tests for the detection of PAD in patients prone to MAC.

Methods

A systematic search (Pubmed, Embase, Web of Science, Cochrane, and Emcare) was performed according to the PRISMA guidelines to identify relevant studies providing data on the performance of bedside tests for the detection of PAD in patients prone to MAC. Studies were included when bedside test were compared to a reference standard. Primary endpoints were the positive and negative likelihood ratios (PLR, NLR). Methodological quality and risk of bias were evaluated using the QUADAS-2 tool.

Results

In total, 23 studies were included in this review. The most commonly evaluated test was the ankle-brachial index (ABI), followed by toe-brachial index (TBI), toe pressure (TP) measurements, and continuous wave Doppler (CWD). The majority of patients were older, male, and had DM. We found that ABI <0·9 was helpful to diagnose PAD, but failed to rule out PAD (NLR >0·2). The same applied for TP (NLR >0·3) and TBI (5 out of 6 studies revealed an NLR >0·2). CWD (loss of triphasic pattern) is reliable to exclude PAD (NLR 0-0·09), but was only validated in two studies. Overall, methodological quality was poor which led to risk of bias in 20 studies.

Conclusion

The diagnosis of PAD in patients prone to MAC remains challenging. The ABI performed reasonably in the diagnosis of PAD, while the CWD (loss of triphasic signal) can be used to rule out PAD. This systematic review showed that test performances were generally poor with serious concerns in methodological quality of the included studies. We therefore counsel against the use of a single bedside test.

Abstract

Research in context

Evidence before this study

Peripheral arterial disease (PAD) is an increasing problem worldwide and is intertwined throughout all medical care. Medial arterial calcification (MAC), common in diabetes mellitus and chronic kidney disease, decreases the accuracy of bedside tests leading to a challenge in daily clinical practice. Early identification of PAD is particularly needed in these patients, allowing for the prompt initiation of cardiovascular risk management (CVRM) and thus reduce the risk of events.

Added value of this study

This systematic review compiled 23 diagnostic studies regarding 5404 patients prone to MAC. Overall, no singular bedside test showed sufficient ability to diagnose and rule out PAD in this patient group. The ankle-brachial index (<0.9 and exclusion of >1.3) seemed useful to diagnose PAD, while the continuous wave Doppler (loss of triphasic signal) provided reliable performance to rule out PAD.

Implications of all the available evidence

Both for ruling in and ruling out PAD, the performance of current bedside tests was disappointing. Generally, risk of bias was high in the included studies with respect to patient selection and interpretation of the bedside tests. These results should strengthen guideline recommendations to renounce the use of a singular bedside test for patients prone to MAC.

Introduction

Peripheral arterial disease (PAD) of the lower extremity is considered a clinical manifestation of systemic atherosclerosis. It is estimated that more than 200 million people are suffering from PAD worldwide.[1] Non-invasive bedside tests such as the ankle-brachial index (ABI) are considered accurate for the diagnosis of PAD. However, the accuracy of bedside testing can be affected by medial arterial calcification (MAC), leading to falsely elevated and unreliable results.[2-6]

MAC is a complex and poorly understood pathological process resulting in incompressible arteries due to calcification of the media of the arterial wall. The increase in arterial wall stiffness impedes bedside diagnostic tools reliant on hemodynamic changes to detect PAD.[7,8] This process is thought to be characteristic of aging, and is expedited in the presence of diabetes mellitus (DM) and chronic kidney disease (CKD).[9-11] Research suggests that MAC is present in approximately one third of patients with DM, and up to 70% in amputations for critical limb ischemia.[12-14] MAC has been shown to be an independent predictor of cardiovascular mortality, while another study found that patients with DM and PAD have an impaired quality of life and an increased risk of adverse cardiac and limb events.[15,16]

While the accurate diagnosis of PAD in patients with MAC can be challenging, timely recognition of critical limb ischemia and initiation of treatment in this patient population is pertinent to reduce delayed wound healing, prevent (major) lower limb amputation, and mortality in diabetic patients with PAD.[17,18] It is expected that the number of patients with DM will increase to nearly 370 million people by 2030 worldwide.[19] Therefore, reliable non-invasive bedside tests to diagnose PAD in patients prone to MAC is of the utmost importance. Recently two systematic reviews were published regarding bedside tests in patients with DM.[20,21] However, bedside diagnostics should be tested in a wider context. MAC causes incompressible arteries and is the underlying problem of the poor performance of the bedside tests. Thus, bedside tests must not only be investigated in patients with DM, but in all patients prone to MAC such as patients with CKD and an ABI >1.3. A complete overview of the diagnostic performance of bedside tests in patients prone to MAC is lacking. Therefore, the aim of this systematic review is to evaluate the reliability of bedside tests compared to reference imaging techniques for diagnosing PAD in patients prone to MAC.

Methods

Search strategy

This study was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines[22] and was not registered in a registry. A literature search was performed in PubMed, Embase (OVID-version), Web of Science, Cochrane Library, and Emcare until February 2021. The search string and justification of the strategy can be found in Supplement S1. Two reviewers (JB, SW) independently screened the titles and abstracts for eligibility of inclusion. Disagreements were resolved in a discussion meeting between two reviewers (JB, SW). Full text articles of the selected abstracts were assessed for inclusion, and the data was extracted.

Selection criteria

We aimed to evaluate the reliability of bedside tests compared to reference tests to diagnose PAD. Bedside tests were considered as any non-invasive technique to detect PAD at the point-of-care. These tests should also be readily available and easy in use. To be eligible for inclusion, studies were required to comply with the following criteria: I) evaluated a bedside (e.g. ABI, TBI, toe pressure, oximetry, pulsations, Doppler waveform) index test compared to a reference test; II) All included patients in the (sub)analyses had to be prone to MAC, defined as DM, CKD or ABI >1·3; III) published in English.

Although digital subtraction angiography (DSA) is regarded as the gold standard for the diagnosis of PAD, it is invasive and carries risks. Magnetic resonance angiography (MRA),[23] computed tomography angiography (CTA),[24] and duplex ultrasonography (DUS)[25] have all been proven to accurately diagnose PAD, and were thus included as reference tests as well. The primary outcomes of interest regarding diagnostic accuracy were the positive likelihood ratio (PLR) and negative likelihood ratio (NLR), because these outcomes reflect the test's ability to rule in or rule out disease (PAD). The interpretation of these likelihood ratios is shown in table 1. Furthermore, sensitivity and specificity of the index tests were also mentioned. We excluded articles that compared bedside tests to each other, reported insufficient data about PLR, NLR, sensitivity, and specificity, investigated serum markers, or were case reports.

Data extraction and quality assessment

Data extraction was performed and verified independently by two investigators (JB, SW). For all articles, extracted data consisted of relevant patient characteristics, the index test performed, correlated imaging modalities, and the diagnostic value (PLR, NLR, sensitivity and specificity) of the index test compared to a reference standard. Measures of test performance such as PLR, NLR, sensitivity, and specificity were extracted and calculated (if necessary) from the accessible data.

Positive likelihood ratio (PLR)	Negative likelihood ratio (NLR)	Interpretation: effect on ability to rule in/rule out disease
>10	<0.1	Large
5-10	0.1-0.2	Moderate
2-5	0.2-0.5	Small
1	1	No change

Table 1: The interpretation of likelihood ratios and their effect on post-test probability of disease.[51]

Methodological quality and risk of bias were assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, specifically designed for diagnostic accuracy studies.[26]

Due to heterogeneity in patient selection, clinical diversity, and the threshold values of index- and reference tests, a meta-analysis could not be performed.

Role of the funding source

There is no direct or indirect funding to declare. Authors JB and SW had access to the data and took the decision to submit for publication.

Results

Overview of studies

An overview of the article selection for this systematic review is reported according to the PRISMA 2020 guidelines (Figure 1).[22] A total of 1017 articles were found, of which 23 studies were eventually included, comprising of 6869 patients. Thirteen of the 23 selected studies included solely patients prone to MAC, described as DM, CKD, or incompressible arteries (n=4038). A sub-analysis specifically assessing test performance in patients prone to MAC was performed in the other ten studies (n=1366). Of the studies selected, 12 were prospective cohort or cross-sectional studies (n=3847), nine were retrospective studies (n=2837), and two were prospective case-control studies (n=185). In the 23 included studies, the number of study participants ranged from 16[27] to 2188,[28] and the ages of subjects at baseline ranged from 53 to 77 years old. The diagnosis of DM was specifically noted in 3693 patients. Duration of DM was mentioned in 12 studies,[28-38] and ranged from 2 to 24 years. Eleven of the included studies described the application of multiple bedside tests per patient population, while twelve studies explored the diagnostic value of a singular bedside test, as shown in table 2. The ABI was the most commonly evaluated bedside test, mentioned in 18 of the 23 included studies. Table 2 describes the 13 other diagnostic parameters discussed in this review. Seventeen studies used DUS as the reference standard for confirming the presence of PAD, and mostly defined >50% stenosis as cut-off value (12

studies). Alternative reference tests included MRA in three studies, CTA in one study, and DSA in two studies.

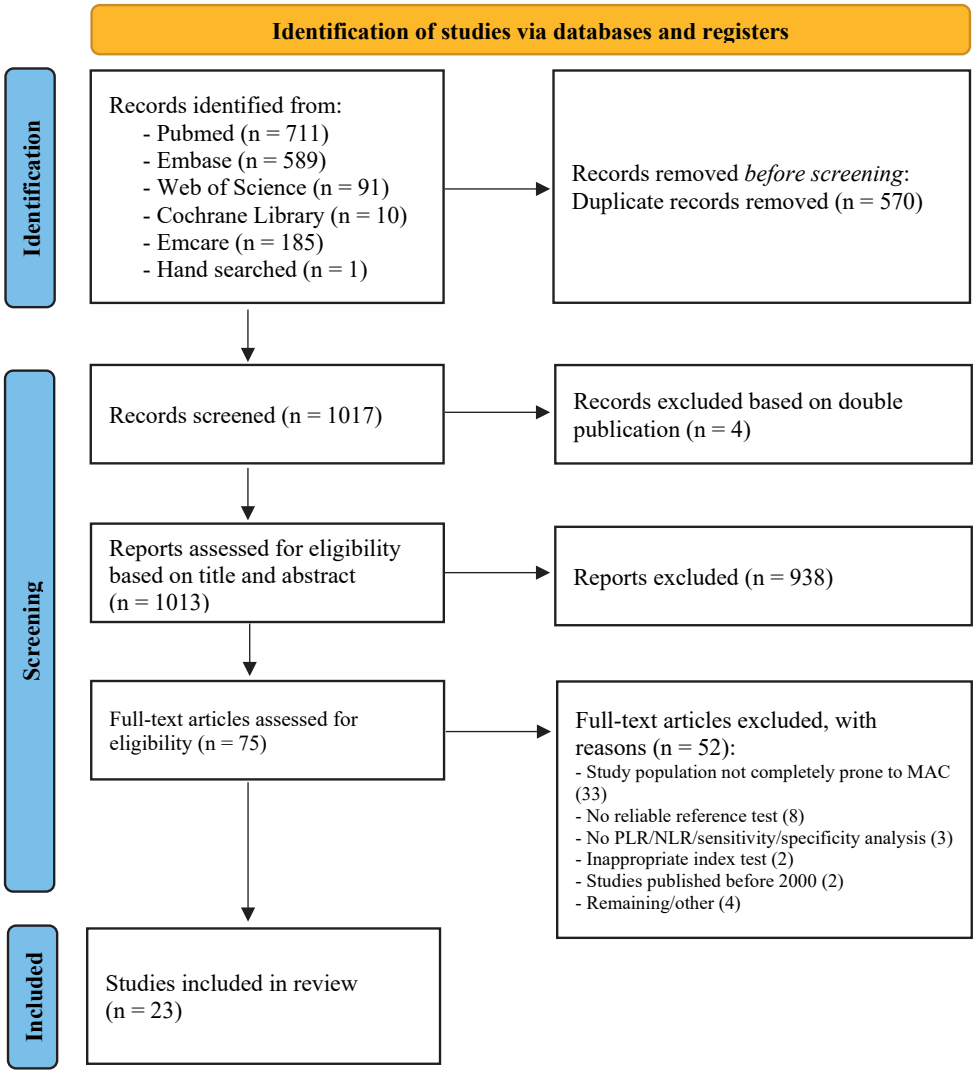

Figure 1: Flow Diagram illustrating article selection process according to the PRISMA guidelines.[22]

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity, patient characteristics)	Index/non-invasive/ point of care test	Reference test; definition of PAD	Index test performance (sensitivity/ specificity/PLR/NLR)	Comments/ opinion
AbuRahma et al.[40] 2020	United States of America	Single-center retrospective cohort study	**Overall** N = 1162 patients with symptomatic PAD Mean age: 65·4 years Gender: not specified 57% of patients had claudication symptoms 43% of patients had limb threatening ischemia **Subgroup analysis** Diabetes (46%: 535 patients) CKD (16%: 186 patients) Age/gender: not specified	ABI <0.9 TBI <0·7	DUS (PAD was defined as >50% stenosis)	*Current results only include the subgroup analysis.* **ABI:** **Diabetics** Sens: 51 (46·1-56·3) Spec: 89 (84·3-92·5) PLR: 4·64 NLR: 0·55 **CKD** Sens: 43 (34·3-52·7) Spec: 95 (88·7-98·4) PLR: 8·6 NLR: 0·6 **TBI:** **Diabetics** Sens: 84 (76·0-90·3) Spec: 58 (46·1-69·9) PLR: 2·0 NLR: 0·28 **CKD** Sens: 77 (61·4-88·2) Spec: 64 (42·5-82·0) PLR: 2·14 NLR: 0·36	The proportion of patients who had TBI is unclear. The proportion of patients who had a reference test is unclear in the specific subgroups.
*Aubert et al.[29] 2014	France	Single-center cross-sectional cohort study	N = 200 patients with diabetes (400 lower limbs) Mean age: 65 years Gender: 80% male Mean duration of DM was 13 years	ABI ≤0·90 or ≥1·30 Foot pulses missing or weak	DUS (PAD was defined as >70% stenosis)	**ABI:** Sens: 42·3% Spec: 80% PLR: 2·11 NLR: 0·72 **Foot pulses missing or weak:** Sens: 69·2% Spec: 71·9% PLR: 2·46 NLR: 0·43	Patients with CKD (eGFR < 30 ml/min) were excluded.

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity, patient characteristics)	Index/non-invasive/ point of care test	Reference test; definition of PAD	Index test performance (sensitivity/ specificity/PLR/NLR)	Comments/ opinion
Buschmann et al.[41] 2018	Austria	Single-center prospective cohort study	**Overall** N = 166 patients suspected of PAD Mean age: 70 years Gender: 76% male **Subgroup analysis** Diabetes (76 patients) Mean age: 70 years Gender: 68% male Hypertension: 89% CVD: 82% CKD: 25%	ABI ≤0·88 ACC_{max} <4·4 m/sec^2 Relative Pulse Slope Index (RPSI) 58·00s^{-1}	DSA (PAD was defined as >50% stenosis)	*Current results only include the subgroup analysis.* **ABI:** Sens: 56% Spec: 83% PLR: 3·29 NLR: 0·53 **RPSI:** Sens: 57% Spec: 95% PLR: 11·4 NLR: 0·45 **ACCmax:** Sens: 57% Spec: 98% PLR: 28·5 NLR: 0·44	Only patients with ABI of ≤0·90 or ≥1·30 and >25% stenosis at DUS were referred for DSA. The proportion is unclear. Patients who were diagnosed with atherosclerotic stenosis of >25% but who did not have a DSA available were excluded. The proportion is unclear.
Clairotte et al.[42] 2009	France	Single-center prospective cohort study	**Overall** N = 146 consecutive patients (292 lower limbs), referred to the physiology department for Doppler ultrasound evaluation of PAD Mean age: 62 years Gender: 68% male **Subgroup analysis** Diabetes (83 patients) Mean age: 63 years Gender: 61% male	Doppler and oscillometric derived ABI <0·90	DUS (PAD was defined as systolic velocity ratio >2·0)	*Current results only include the subgroup analysis.* **Doppler ABI:** Sens: 54% Spec: 97% PLR: 17 NLR: 0·47 **Oscillometric ABI:** Sens: 29% Spec: 96% PLR: 7·9 NLR: 0·74	Unblinded study The NLR was recalculated by the present research group since the NLR results in the original paper were incorrect.

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity, patient characteristics)	Index/non-invasive/ point of care test	Reference test; definition of PAD	Index test performance (sensitivity/ specificity/PLR/NLR)		Comments/ opinion
Faglia Ezio et al.[30] 2010	Italy	Single-center prospective cohort study	N = 261 patients with diabetes and rest pain and/or foot ulcer in 1 limb Mean age: 73 years Gender: 67% male Mean duration of DM was 18 years	Ankle pressure (AP) <70 mm Hg Transcutaneous oxygen tension ($TcPO_2$) <50 mm Hg	DSA (PAD was defined as >50% stenosis)	**AP:** Sensitivity: 33% Spec: N/A PLR: N/A NLR: N/A **$TcPO_2$ <30 mmHg:** Sensitivity: 82% Spec: N/A PLR: N/A NLR: N/A **$TcPO_2$ <50 mmHg:** Sensitivity: 100% Spec: N/A PLR: N/A NLR: N/A		Unblinded study Only patients with AP <70 mm Hg and/ or $TcPO_2$ <50 mm Hg underwent DSA. All included patients had >50% stenosis on DSA probably due to the selection of patients. As a result, it was not possible to calculate specificity. AP not measurable in 42% patients (13% arterial calcifications).
Homza et al.[31] 2019	Czech Republic	Single-center prospective cohort study	N = 62 patients with diabetes (124 limbs) Mean age: 68 years Gender: 74% male Mean duration of DM was 8 years	Doppler ABI using highest ankle pressure (hABI) <0·9 or >1·4 Doppler ABI using lowest ankle pressure (lABI) <0·9 or >1·4 Oscillometric ABI <0·9 or >1·4	DUS (PAD was defined as >50% stenosis)	**Higher ABI:** Sens: 67% Spec: 75% PLR: 2·68 NLR: 0·44 **Oscillometric ABI:** Sens: 61% Spec: 94% PLR: 10·17 NLR: 0·41	**Lower ABI:** Sens: 87% Spec: 76% PLR: 3·63 NLR: 0·17	Patients with critical limb ischemia were excluded (Rutherford 4-6).
Hur et al.[32] 2018	South Korea	Single-center retrospective cohort study	N = 324 patients with diabetes Mean age: 63 years Gender: 59% male Mean duration of DM was 11 years	ABI <0·9	DUS (PAD was defined as >50% stenosis)	**ABI:** Sens: 17% Spec: 99% PLR: 17 NLR: 0·84		Patients with ABI >1·40 were excluded.

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity, patient characteristics)	Index/non-invasive/ point of care test	Reference test; definition of PAD	Index test performance (sensitivity/ specificity/PLR/NLR)		Comments/ opinion
Janssen et al.[33] 2005	Germany	Single-center prospective cohort study	N = 106 patients with diabetes who were hospitalized Mean age: 72 years Gender: 68% male Mean duration of DM was 20 years	ABI <0·9 Ankle-Brachial Pressure (ABP) <70 mmHg Pulsatility index (PI) <1·2	The need for revascularization on the basis of a) clinical findings and b) arteriographic findings.	**ABI:** Sens: 71% Spec: 42% PLR: 1·22 NLR: 0·69 **ABP:** Sens: 30% Spec: 89% PLR: 2·73 NLR: 0·79	**PI:** Sens: 87% Spec: 62% PLR: 2·29 NLR: 0·21	In total, 54% of patients had medial arterial calcification (assessment on X-ray).
Li et al.[28] 2015	China	Single-center cross-sectional cohort study	**Overall** N = 2188 patients with diabetes Mean age: 61 years Gender: 54% male **Subgroup analysis:** ABI > 1·3 (175 patients) Mean age: 63 years Gender: 59% male Mean duration of DM was 9 years	ABI >1·45	DUS and MRA 438 underwent DUS/MRA due to abnormal ABI: - 314 patients had DUS - 124 patients had MRA	*Current results only include the subgroup analysis.* **ABI >1·45:** Sens: 65% Spec: 85% PLR: 4·33 NLR: 0·41		The optimal ABI threshold was calculated (determined with Youden index). Threshold of reference test to diagnose PAD was unclear.

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity, patient characteristics)	Index/non-invasive/ point of care test	Reference test; definition of PAD	Index test performance (sensitivity/ specificity/PLR/NLR)		Comments/ opinion
*Normahani et al.[39] 2020	United Kingdom	Multicenter prospective cohort study	N = 305 patients with diabetes (recruited from diabetic foot clinics) Mean age: 72 years Gender: 68% male Mean duration of DM was 17 years CKD was present in 17% of patients	Pulse palpation (absence of dorsalis pedis or posterior tibial artery pulse) Audible Doppler (monophasic or absent signal in either vessel) Visual Doppler with handheld Doppler device (monophasic or absent signal in either vessel) ABI < 0.9 TBI < 0.75 TcPO2 <40 mmHg PAD-scan (the presence of an occlusion, venous like slow flow, monophasic waveform or a biphasic waveform with adverse features in either vessel)	DUS (PAD was defined as >50% stenosis)	**ABI** Sens: 60% Spec: 75% PLR: 2.46 NLR: 0.53 **Audible Doppler** Sens: 74% Spec: 76% PLR: 3.04 NLR: 0.35 **Visual Doppler** Sens: 83% Spec: 75% PLR: 3.28 NLR: 0.23 **Pulse palpation** Sens: 43% Spec: 81% PLR: 2.22 NLR: 0.71	**TBI** Sens: 60% Spec: 86% PLR: 4.26 NLR: 0.47 **TcPO2** Sens: 31% Spec: 79% PLR: 1.43 NLR: 0.88 **PAD-scan** Sens: 95% Spec: 77% PLR: 4.06 NLR: 0.07	PAD-scan was performed using a portable ultrasound machine with a linear 6-14Hz transducer. A 'normal' biphasic waveform indicated no PAD. However, several adverse features are mentioned in this study leading biphasic waveforms to abnormal: - Spectral broadening - Infilling of the spectral window - Long diastolic forward flow - Slow systolic rise time

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity, patient characteristics)	Index/non-invasive/ point of care test	Reference test; definition of PAD	Index test performance (sensitivity/ specificity/PLR/NLR)		Comments/ opinion
Perriss et al.[43] 2005	Denmark	Single-center retrospective cohort study	N = 104 patients with end-stage renal failure who underwent CE-MRA of the lower extremity Mean age: 53 years Gender: 71% male 80 asymptomatic patients 24 symptomatic patients (16 claudication, 5 ulcers, 3 other symptoms) **Study population consisted of 69 patients (had both ABI and MRA)**	ABI <0·90	CE-MRA (PAD was defined as >50% stenosis)	**ABI in asymptomatic patients (n=48):** Sens: 56·3% Spec: 87·5% PLR: 4·50 NLR: 0·50 **ABI in combined patients (n=69):** Sens: 74·3% Spec: 85·3% PLR: 5·05 NLR: 0·30	**ABI in symptomatic patients (n=21):** Sens: 89·5% Spec: 50% PLR: 1·79 NLR: 0·21	In 80 out of 104 patients, the indication for MRA was pretransplant evaluation (asymptomatic). 19 of 80 asymptomatic patients had incompressible vessels (24%).
Premalatha et al.[34] 2002	India	Single-center prospective cohort study	N = 100 hospital admitted patients with diabetes and severe foot infections Mean age: 60 years Gender: not specified Mean duration of DM was 12 years	ABI <0·90	DUS (PAD was defined as >50% stenosis)	**ABI:** Sens: 70·6% Spec: 88·5% PLR: 6·14 NLR: 0·33		Six patients with calcification of peripheral vessels were excluded (unclear how presence of calcification was assessed).

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity, patient characteristics)	Index/non-invasive/ point of care test	Reference test; definition of PAD	Index test performance (sensitivity/ specificity/PLR/NLR)		Comments/ opinion
Ro et al.[44] 2013	South Korea	Single-center retrospective cohort study	N = 97 patients (194 legs), who had coincidentally undergone CTA, PPG, ABI and CWD for the evaluation of PAD Mean age: 67 years Gender: 91% male **Subgroup analysis** Diabetes (44 patients, 88 legs) Mean age/gender: not specified	ABI <0.90 Continuous-Wave Doppler (CWD), considered positive if: (1) Loss of triphasic pattern, or (2) Decreased amplitude of more than 50% compared with the contralateral side, or (3) Loss of reverse flow component. Photoplethysmography (PPG) wave form, considered positive if: (1) Loss of dicrotic Notch, or (2) Decreased amplitude of more than 50% compared with contralateral side, or (3) rounding of peaks compared with contralateral side.	CTA (PAD was defined as >50% stenosis)	*Current results only include the subgroup analysis.* **ABI:** Sens: 74·7(64-83) Spec: 88.9(57-98) PLR: 6·73 NLR: 0·28 **PPG:** Sens: 78·5 (68-86) Spec: 89% (57-98) PLR: 7·14 NLR: 0·24	**CWD:** Sens: 97·5 (91-99) Spec: 66·7 (35-88) PLR: 2·93 NLR: 0·04	
Saunders et al.[27] 2019	United Kingdom	Single-center retrospective cohort study	N = 16 patients (32 limbs) Mean age: 66 years Gender: 94% male Selection criteria included confirmed incompressible vessels (defined as persistent flow with blood pressure cuff inflated to >220 mm Hg) and MRA within the preceding 6 months with no interval arterial intervention. All patients had tissue loss	Vascular early warning system (VEWS) device	MRA (PAD was defined as >50% stenosis)	**VEWS ≤0·94:** Sens: 73% Spec: 80% PLR: 3·65 NLR: 0·34		VEWS functions by using red and infrared optical sensors placed on the toe and dorsum of the foot to register changes in blood volume within the microvasculature that occur during a gravity-induced functional test.

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity, patient characteristics)	Index/non-invasive/ point of care test	Reference test; definition of PAD	Index test performance (sensitivity/ specificity/PLR/NLR)	Comments/ opinion
Sonter et al.[47] 2017	Australia	Single-center prospective cohort study	**Overall** N = 90 patients (PAD analysis) Mean age: 73 years Gender: 58% male **Subgroup analysis** Diabetes (50 patients) Mean age/gender: not specified	TBI <0·70 Toe pressure <70 mmHg	DUS (PAD was defined as >50% stenosis)	*Current results only include the subgroup analysis.* **TBI:** Sens: 73·9% Spec: 66·7% PLR: 2·22 NLR: 0·39 **Toe pressure:** Sens: 45·8% Spec: 100% PLR: infinite NLR: 0·54	32% of patients had medial arterial calcification. However, it was unclear how presence of medial arterial calcification was assessed. It was unclear if TBP <70 was pre-specified.
Tehan et al.[45] 2016	Australia	Single-center prospective cross- sectional case-control study	**Overall** N = 117 patients (PAD analysis) Mean age: 73 years Gender: 63% male **Subgroup analysis** Diabetes (72 patients) Mean age: 72 years Gender: 65% male	ABI ≤ 0·90 or > 1·4 TBI ≤ 0·70 Continuous-Wave Doppler (CWD), considered positive if monophasic pattern in either the dorsalis pedis or posterior tibial arteries, demonstrated by low-resistance, slow systolic acceleration and no diastolic flow reversal	DUS (PAD was defined as >50% stenosis)	*Current results only include the subgroup analysis.* **ABI:** Sens: 45·2% Spec: 92·7% PLR: 6·17 NLR: 0·59 **TBI:** Sens: 63·6% Spec: 82·1% PLR: 3·55 NLR: 0·44 **CWD:** Sens: 74·2% Spec: 92·9% PLR: 10·39 NLR: 0·28	Ten percent of patients with diabetes had incompressible ankle pressures.

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity, patient characteristics)	Index/non-invasive/ point of care test	Reference test; definition of PAD	Index test performance (sensitivity/ specificity/PLR/NLR)		Comments/ opinion
Tehan et al.[48] 2017	Australia	Single-center retrospective case-control study	**Overall** N = 394 participants (suspected PAD) Mean age: 77 years Gender: 61% male **Subgroup analysis** Diabetes (176 patients) Mean age: 75 years Gender: 65% male	Toe pressure < 97 mmHg	DUS (PAD was defined as >50% stenosis)	*Current results only include the subgroup analysis.* **Toe pressure:** Sens: 73·7% Spec: 72·4% PLR: 2·67 NLR: 0·36		TP cutoff value was calculated based on ROC curves. 27% of patients had calcification of peripheral vessels visualised on DUS. However, it was unclear how presence of calcification was assessed.
Tehan et al.[46] 2018	Australia	Single-center retrospective case-control study	**Overall** N = 160 patients (278 limbs) with suspected PAD Mean age: 73 years Gender: 69% male **Subgroup analysis** Diabetes (107 patients) Mean age: 71 years Gender: 73% male	ABI ≤ 0·9 Post-exercise ABI: - Post exercise ABI ≤ 0·9 - >20% reduction compared to resting ABI - >30mmHg reduction compared to Resting systolic ankle pressure	DUS (PAD was defined as >50% stenosis)	*Current results only include the subgroup analysis.* **ABI:** Sens: 53·8% Spec: 92·9% PLR: 7·53 NLR: 0·50 **Post-exercise ABI (≤ 0·9):** Sens: 69·6% Spec: 80·0% PLR: 3·48 NLR: 0·38	**Post-exercise (>20%) reduction compared to resting ABI:** Sens: 59·6% Spec: 61·1% PLR: 1·53 NLR: 0·66 **Post-exercise (>30mmHg) reduction in systolic ankle pressure:** Sens: 51·1% Spec: 25·0% PLR: 0·68 NLR: 1·96	28% of patients had incompressible ankle pressures. 31% of patients with diabetes had MAC visualised on CDUS. MAC was determined based on DUS, but it is unclear which criteria were used. The PLR/NLR for the *post-exercise (>30mmHg) reduction in systolic ankle pressure* were recalculated by the present research group since the PLR/ NLR results in the original paper were incorrect.

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity, patient characteristics)	Index/non-invasive/ point of care test	Reference test; definition of PAD	Index test performance (sensitivity/ specificity/PLR/NLR)		Comments/ opinion
Tehan et al.[49] 2018	Australia	Single-center retrospective case-control study	**Overall** N = 396 patients (suspected PAD) Mean age: 77 years Gender: 61% **Subgroup analysis** Diabetes (176 patients) Mean age: 75 years Gender: 65% male **Subgroup analysis** Medial arterial calcification (98 patients) Mean age/gender: not specified	Continuous wave Doppler (CWD): monophasic or absent signal.	DUS (PAD was defined as >50% stenosis)	*Current results only include the subgroup analyses.* **CWD (subgroup DM):** Sens: 82·8% Spec: 88·3% PLR: 7·09 NLR: 0·19 **CWD (subgroup MAC):** Sens: 82·9% Spec: 81·8% PLR: 4·56 NLR: 0·21		Unblinded study MAC was present in 25% of the patients with diabetes. Subgroup analysis of MAC included both patients with and without diabetes. MAC was determined based on DUS, but it is unclear which criteria were used. Biphasic signals were considered as multiphasic (normal).
Ugwu et al.[35] 2021	Nigeria	Single-center cross-sectional cohort study	N = 163 patients with diabetes (319 legs) with clinical suspicion of lower extremity PAD Mean age: 56 years Gender: 47% male Mean duration of DM was 8·6 years	ABI < 0·9	DUS (PAD was defined as >50%) The severity of stenosis was graded as follows: (1) 50–75% = mild stenosis (2) 76–99% = moderate stenosis (3) complete occlusion = severe stenosis	**ABI (overall):** Sens: 78·46% Spec: 91% PLR: 8·72 NLR: 0·24 **ABI (moderate stenosis):** Sens: 93% Spec: 91% PLR: 10·33 NLR: 0·08	**ABI (mild stenosis):** Sens: 54% Spec: 91% PLR: 6 NLR: 0·51 **ABI (severe stenosis):** Sens: 100% Spec: 91% PLR: 11·11 NLR: 0	Seven patients with ABI >1·3 were excluded. Unclear if study was prospective or retrospective.

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity, patient characteristics)	Index/non-invasive/ point of care test	Reference test; definition of PAD	Index test performance (sensitivity/ specificity/PLR/NLR)		Comments/ opinion
*Vriens et al.[36] 2018	United Kingdom	Single-center prospective cohort study	N = 60 patients with diabetes-related foot ulceration Mean age: 66 years Gender: 75% male Mean duration of DM was 2 years Comorbidity: - 38% CKD	Palpation of pulses ABI <0·9 or >1·3 Ankle pressure: <70 mmHg Toe pressure: <50 mmHg TBI: <= 0·75 TcPO2: < 60mmHg Pole test (the height - in cm - at which the Doppler signal was lost while elevating the leg) Waveform analysis by DUS (monophasic and/ or damped waveforms)	DUS (PAD was defined as >50% stenosis)	**Palpation/pulses:** Sens: 55% Spec: 60% PLR: 1·38 NLR: 0·75 **Ankle pressure:** Sens: 47% Spec: 79% PLR: 2·25 NLR: 0·67 **TBI:** Sens: 89% Spec: 45% PLR: 1·62 NLR: 0·24 **Pole test:** Sens: 28% Spec: 97% PLR: 10·29 NLR: 0·74	**ABI:** Sens: 68% Spec: 59% PLR: 1·69 NLR: 0·53 **Toe pressure:** Sens: 45% Spec: 97% PLR: 17·55 NLR: 0·56 **TcPO2:** Sens: 28% Spec: 66% PLR: 0·81 NLR: 1·10 **Waveform:** Sens: 85% Spec: 100% PLR: infinite NLR: 0·15	Waveform analysis was not blinded to the reference test.

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity, patient characteristics)	Index/non-invasive/ point of care test	Reference test; definition of PAD	Index test performance (sensitivity/ specificity/PLR/NLR)		Comments/ opinion
Williams et al.[37] 2005	United Kingdom	Single-center prospective case-control study	**Overall** N = 68 individuals (130 limbs) with diabetes were screened for PAD (without critical ischemia) Mean age/gender: not specified **Subgroup analysis** Diabetes (89 patients) Mean age: 63-69 years Gender: 74% male Mean duration of DM was 11-24 years	Foot pulse: absence of one or both foot pulses. ABI < 0·9 TBI <0·75 Continuous wave Doppler (CWD): loss of triphasic signal.	DUS (PAD was defined as significant velocity change and flow disturbance locally that resulted in loss of reverse flow distally, caused by occlusions or stenosis)	*Current results only include the subgroup analyses.* **Diabetic no neuropathy (n=32 limbs)** **Foot pulse:** Sens: 87% Spec: 53% PLR: 1·85 NLR: 0·25 **TBI:** Sens: 91% Spec: 65% PLR: 2·6 NLR: 7·2 **Diabetic neuropathy (n=57 limbs)** **Foot pulse:** Sens: 81% Spec: 56% PLR: 1·84 NLR: 0·34 **TBI:** Sens: 100% Spec: 61% PLR: 2·56 NLR: 0	**ABI:** Sens: 100% Spec: 88% PLR: 8·33 NLR: 0 **CWD:** Sens: 100% Spec: 92% PLR: 12·5 NLR: 0 **ABI:** Sens: 53% Spec: 95% PLR: 10·6 NLR: 0·49 **CWD:** Sens: 94% Spec: 66% PLR: 2·76 NLR: 0·09	Active foot disease, rest pain, or signs suggestive of lower limb critical ischemia were excluded. The definition of significant velocity change in DUS was not specified.

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity, patient characteristics)	Index/non-invasive/ point of care test	Reference test; definition of PAD	Index test performance (sensitivity/ specificity/PLR/NLR)	Comments/ opinion
Zhang et al.[38] 2010	China	Single-center retrospective case-control study	N = 184 patients with diabetes were screened for PAD Mean age: 63 years Gender: 74% male Mean duration of DM was 11·5 years	ABI < 0·9	DUS (Large plaque >10 mm^2 with 100% increase in peak systolic velocity)	**ABI:** Sens: 93·75% Spec: 88·16% PLR: 7·92 NLR: 0·07	Patients who had one leg with low ABI and one leg with high ABI were excluded.

Table 2: Evidence table of all included studies.

Studies of high methodological quality are marked with asterisks (*).
ABI = Ankle-Brachial Index, ABP = Ankle-Brachial Pressure, ACCmax = Maximal Systolic Acceleration, AP = Ankle Pressure, CKD = Chronic Kidney Disease, CTA = Computed Tomography Angiography, CWD = Continuous Wave Doppler, DM = Diabetes Mellitus, DSA = Digital Subtraction Angiography, DUS = Duplex Ultrasonography, MRA = Magnetic Resonance Angiography, PAD = Peripheral Arterial Disease, PI = Pulsatility index, PPG = Photoplethysmography, RPSI = Relative Pulse Slope Index, TBI = Toe-Brachial Index, TcPO2 = Transcutaneous Oxygen Tension, and TP = Toe Pressure

Quality assessment of included studies

The results of the quality assessment are illustrated in table 3. Only three[29,36,39] of the included studies were of high methodological quality (i.e. low risk of bias in all domains assessed). Risk of bias was generally high or unclear with respect to the selection of participants, and the conduct and interpretation of the index tests and reference standards. Applicability concerns were generally low with respect to the selection of patients, the index- and reference tests.

Author & year	Risk of Bias				Applicability Concerns		
	Patient selection	Index test	Reference standard	Flow & timing	Patient selection	Index test	Reference standard
AbuRahma 2020[40]	Unclear	Low	Unclear	High	Low	Low	Low
Aubert 2013[29]	Low	Low	Low	Low	Low	Low	Low
Buschmann 2018[41]	Low	High	Unclear	High	Low	Low	Low
Clairotte 2009[42]	High	High	High	Low	Low	Low	Low
Faglia Ezio 2010[30]	High	Low	High	Low	Low	Low	Low
Homza 2019[31]	Low	Low	Unclear	Low	Low	Low	Low
Hur 2018[32]	Low	Low	Unclear	Low	Unclear	Low	Low
Janssen 2005[33]	High	Low	Unclear	Low	Low	Low	Unclear
Li 2015[28]	High	High	Unclear	High	Unclear	High	Low
Normahani 2020[39]	Low	Low	Low	Low	Low	Low	Low
Perriss 2005[43]	High	Unclear	Unclear	High	High	Low	Low
Premalatha 2002[34]	High	Low	Unclear	High	Low	Low	Low
Ro 2013[44]	High	Unclear	Unclear	Low	Low	Low	Low
Saunders 2019[27]	High	Unclear	Unclear	Low	Low	Low	Low
Sonter 2017[47]	Low	Unclear	Unclear	Low	Low	Low	Low
Tehan 2016[45]	Low	Low	Unclear	Low	Low	Low	Low
Tehan 2017[48]	High	High	Unclear	Low	Low	Low	Low
Tehan 2018[46]	High	Low	Unclear	Low	Low	Low	Low
Tehan 2018[49]	High	Low	High	Low	Low	Low	Low
Ugwu 2021[35]	Low	Low	Unclear	Low	Low	Low	Low
Vriens 2018[36]	Low	Low	Low	Low	Low	Low	Low
Williams 2005[37]	High	Low	Unclear	Low	High	Low	Low
Zhang 2010[38]	Low	Unclear	Unclear	High	High	Low	Low

Table 3: Methodological assessment of all included studies based on QUADAS-2 tool.
H = High = if any of the signaling questions for a domain were answered with 'no', potential for bias existed and was graded as high.
L = Low = if all signaling questions for a domain were answered with 'yes', the risk of bias was judged as low.
U = Unclear = this category was only used if insufficient data was reported to permit a judgment.

Ankle-brachial index

Eighteen studies evaluated the ABI to diagnose PAD in patients prone to MAC.[28,29,31-46] In these studies, 10 different variables were investigated (table 4 shows an overview). In studies including patients with an ABI >1·3, the PLR ranged between 1·22 and 17, and the NLR ranged between 0 and 0·69 for an ABI with a threshold of <0·90. When an ABI of <0·9 or >1·3 to 1·4 was defined as abnormal, the PLR and NLR ranges changed to 1·69-6·17 and 0·44-0·72, respectively.

Ankle pressure

Three studies mentioned an absolute ankle pressure of <70mmHg as the threshold for diagnosing PAD. In two of these studies, a PLR of 2·25–2·73 and an NLR of 0·67–0·79 were found to detect PAD.[30,33,36] It was not possible to calculate the PLR/NLR as a result of the selection of patients in one study. All included patients had >50% stenosis on DSA, so only the sensitivity of 33% could be given in this study.[30] A post-exercise reduction of >30mmHg in systolic ankle pressure showed a lower PLR of 0·68 to detect PAD.[46]

Toe-brachial index; toe pressure

Six studies investigated the TBI as an index test for PAD (with cut-off values of below 0·70 and 0·75).[36,37,39,40,45,47] In these studies, PLRs ranged from 1·62 to 4·26. NLRs fluctuated between 0 and 0·47. In the three studies that evaluated toe pressure, different cut-off values were used.[36,47,48] Vriens et al. used a pressure below 50 mmHg as indicator for PAD, leading to a PLR of 17·55 and an NLR of 0·56.[36] Sonter et al. studied a pressure below 70 mmHg, with an infinite PLR and an NLR of 0·54.[47] Tehan et al. used a pressure below 97 mmHg, resulting in a PLR of 2·67 and an NLR of 0·36.[48]

Palpable pulsations

Four studies explored the palpation of foot pulses as a bedside test.[29,36,37,39] Since these studies described different criteria for the diagnosis of PAD, these articles will be described separately. Aubert et al. regarded missing or weak foot pulses as an indicator for PAD, leading to a PLR of 2·46 and NLR of 0·43.[29] Vriens et al. used the absence of foot pulses as PAD criterion, resulting in a PLR of 1·38 and an NLR of 0·75.[36] Williams et al. and Normahani et al. considered the absence of one or both foot pulses as diagnostic of PAD. This resulted in PLR/NLR of 1.84/0.31 and 2.22/0.71 respectively.[37,39]

Waveform analysis

Waveform analysis, measured at the dorsalis pedis- or posterior tibial artery, is described in six articles (two studies investigated two techniques).[36,37,39,44,45,49] Visual waveform analysis was conducted using a Continuous Wave Doppler (CWD) device in five studies, a Duplex ultrasound scanning (DUS) device in two studies, and photoplethysmography in one study. Abnormal waveform was heterogeneously defined. Two studies by Tehan et al. and

Index test with threshold	ABI >1·3 included/ excluded in study population	Number of studies	Number of patients	PLR	NLR	Sensitivity	Specificity
ABI < 0·9[32,35]	Excluded	2	487	8·72-17	0·24-0·84	17%-78·46%	91%-99%
ABI < 0·9[33,34,37-40,42-44,46]	Included	10	1801	1·22-17	0-0·69	53%-100%	42%-95%
ABI <0·9 or >1·3-1·4[29,31,36,45]	Included	4	394	1·69-6·17	0·44-0·72	42·3%-68%	59%-92·7%
ABI < 0·88[41]	Included	1	76	3·29	0·53	56%	83%
Oscillometric ABI < 0.9[42]	Included	1	83	7·9	0·74	29%	96%
Oscillometric ABI <0·9 or >1·4[31]	Included	1	62	10·17	0·41	61%	94%
Lower ABI <0·9 or >1·4[31]	Included	1	62	3·63	0·17	87%	76%
ABI >1·45 (Only patient with ABI >1·3 were included)[28]	Included	1	175	4·33	0·41	65%	85%
Post-exercise ABI (≤0·9)[46]	Included	1	107	3·48	0·38	69·6%	80·0%
Post-exercise (>20%) reduction compared to resting ABI[46]	Included	1	107	1·53	0·66	59·6%	61·1%

Table 4: an overview of the different ABI variables to diagnose PAD.

Normahani et al. described PAD as the presence of a monophasic or dampened waveform using CWD, with a PLR ranging from 3·28 to 10·39 and an NLR of 0·19 to 0·28.[39,45,49] Vriens et al. described an infinite PLR and an NLR of 0·15 for the detection of PAD by DUS waveform analysis, defined as a monophasic or damped waveform. Note that waveform analysis was not blinded to the reference test in this study.[36] Loss of a triphasic pattern is another parameter for defining PAD and was investigated in two studies using CWD. The PLR varied between 2·76 and 12·5 and the NLR between 0 and 0·09.[37,44] The detection of PAD by photoplethysmography waveform assessment showed a PLR of 7·14 and NLR of 0·24.[44] Normahani et al. investigated the PAD-scan (waveform analysis performed using DUS), this is explained in detail in table 2. This technique showed a PLR of 4.06 and NLR of 0.07.[39]

Transcutaneous oxygen pressure

Three studies investigated the reliability of transcutaneous oxygen pressure (TcPO2).[36,39] Vriens et al. regarded a pressure below 60 mmHg as PAD, resulting in a PLR of 0·81 and an NLR of 1·10.[36] Normahani et al. used a pressure below 40 mmHg, which showed a PLR of 1.43 and NLR of 0.88.[39] Faglia Ezio et al. studied pressures below 30 and 50 mmHg, with a sensitivity of 82% and 100% respectively. Since all patients in this study had PAD (probably due to patient selection), specificity, PLR and NLR could not be calculated.[30]

Other

Novel arterial Doppler flow parameters, the maximum systolic acceleration (ACCmax) and the relative pulse slope index (RPSI) were explored by Buschmann et al.[41] The ACCmax, defined as maximum slope of the velocity curve in the systolic phase detected PAD with a PLR of 28·5 and NLR of 0·44 when adopting a cut-off value of $<4{\cdot}4 m/sec^2$. Janssen et al. described a colour duplex ultrasonography parameter, pulsatility index (PI), as a PAD diagnostic test.[33] PI is defined as "the ratio of the maximum vertical excursions of the Doppler", and showed a PLR of 2·29 and NLR of 0·21 for a threshold of <1.2. A pole test, the height in centimeters at which the Doppler signal can no longer be detected while passively elevating the leg, is assessed in one article and showed a PLR 10·29 and NLR 0·74.[36] Lastly, a study by Saunders et al. described a Vascular Early Warning System device (VEWS).[27] The VEWS device functions by measuring changes in blood volume in the microvasculature of the foot, as detected by infrared optical sensors. This method showed a PLR of 3·65 and NLR 0·34 when a cut-off of ≤0·94 was selected to detect PAD.

Discussion

To the best of our knowledge, this is the first systematic review on bedside tests to diagnose PAD in patients prone to MAC. While MAC can hamper the performance of bedside tests to diagnose PAD, only 23 studies investigated the accuracy of bedside tests in patients prone to MAC. Most studies were performed in Western countries, and included predominantly older males with DM. The included studies often contained small study populations and had flaws in methodological quality, raising serious concerns about their reliability. Overall, the performances of the different bedside tests were generally disappointing and highly variable between studies.

Worldwide, the ABI is the most frequently used bedside test to diagnose PAD.[50] In 18 studies that evaluated the ABI, 10 different ABI variables were investigated (Table 4) in which the ABI threshold or study population (ABI >1·3 included or excluded) differed. In most studies an ABI <0·90 was defined as abnormal, followed by four studies that considered an ABI of <0·90 and >1·3–1·4 as PAD. Two studies investigated an ABI threshold of 0·9 and excluded patients with an ABI >1·3,[32,35] which is in line with current guidelines[2,50] in which patients with an ABI >1·3–1·4 should undergo alternative tests. In these two studies,[32,35] the ABI could accurately rule in PAD with a PLR of 8·72–17, but it failed to rule out PAD (NLR 0·24–0·84). The same pattern was seen in all 18 studies, where 16 studies showed an insufficient NLR >0·2 (small effect on ability to rule out PAD). Generally, including patients with ABI >1·3 resulted in a lower performance to diagnose PAD (PLR 1·22–17). Of note, only one study investigated the use of the lowest ankle pressure to calculate the ABI, which lead to an improved performance of the test (compared to the highest ankle pressure).[31]

Since digital arteries are less affected by MAC, the measurement of toe pressure may be more reliable in patients with DM or CKD. Six studies investigated the use of TBI to diagnose PAD, but none of these studies found a moderate or large effect on the ability to diagnose PAD (PLR > 5).[36,37,40,45,47] A mixed performance was seen in the ability to rule out PAD, with NLRs of 0–0·47. However, only one small study (N=57 limbs)[37] had a large effect on the probability to exclude disease and resulted in this outlier (NLR 0). The other five studies did not have an accurate diagnostic effect to rule out PAD (NLR <0·2).[36,40,45,47] In the three studies evaluating absolute toe pressure, it was remarkable to note that each study used a different threshold.[36,47,48] A pressure of <50 mmHg appeared to be very accurate in diagnosing PAD (PLR 17·55), but provided poor performance to rule out disease (NLR 0·56).[36] Raising the cut-off values to 70 and 97 mmHg resulted in a better, however still insufficient, ability to exclude PAD (NLR 0·54 and 0·36).[47,48]

Palpation of arterial pulsations during physical examination forms another cornerstone of clinical practice. While palpation of arterial pulsations may appear to be an attractive

bedside test due to the inexpensive and readily applicable nature, the data supporting this method show limited diagnostic utility.[29,36,37,39] In these studies, different definitions were regarded as abnormal: I) missing or weak, [29] II) absence of one or both foot pulses,[37,39] and III) absent of pedal pulses.[36] Either way, deviations in palpation of arterial pulsations showed a poor performance to diagnose PAD in patients prone to MAC (PLR 1·38–2·46).[29,36,37] Moreover, one study made the distinction between the presence (dorsalis pedis artery or posterior tibial artery) and absence of pedal pulses. This study showed that the presence of a palpable pedal pulse was insufficient to exclude PAD (NLR 0·75).[36]

Various other index bedside tests were investigated in the studies included in this review. Visual waveform analysis performed by continuous waveform Doppler (CWD) device showed the best test performance to rule out PAD with a relatively small variation in NLR (0–0·28).[37,39,44,45,49] It is important to note that in three of the five studies PAD could not be definitively excluded (NLR >0·2), while three studies demonstrated a moderate to proficient ability to diagnose PAD (PLR >5).[37,45,49] However, the definition of an abnormal test was not consistent between these studies. In three studies, the presence of a monophasic or dampened waveform indicated PAD,[39,45,49] while a loss of a triphasic pattern was described as abnormal in the other two studies.[37,44] When a loss of a triphasic pattern was used with CWD, PAD could be accurately ruled out (NLR 0–0·09).[37,44] Although very reliable, this cut-off would be hard to implement in daily clinical practice, since the majority of patients prone to MAC have dampened, monophasic, or biphasic waveforms. Therefore, the addition of a loss of triphasic pattern with CWD as criterium for PAD will be of diminished value in clinical practice. Notably, only one of the studies included in this review mentioned the use of audible waveform analysis, with limited performance (PLR 3.04 and NLR 0.35).[39] The PAD-scan waveform assessment, as described by Normahani et al. seems promising and can accurately rule out PAD (NLR 0.07), however this bedside test is only investigated in one study and could be complex to interpretate. [39] Furthermore, the evidence supporting the ankle pressure[30,33,36] and TcPO2[30,36,39] as a bedside test in patients with suspected MAC was sparse and poor results were found.

For clinicians, diagnosing PAD in patients with DM or CKD presents a major clinical challenge. Due to comorbidities such as neuropathy, patients frequently have atypical or no symptoms such as ischemic rest pain.[8] Also, clinical examination provides insufficient reliable information to determine which patients have PAD or need further investigations. Additionally, this review shows that current index tests lack the ability to reliably diagnose or rule out PAD. All these considerations stress the importance of the need for a better bedside test, chiefly since early revascularization in patients with critical limb ischemia is essential to decrease future complications, and minimize morbidity in this patient group.[17,18] Moreover, early identification of diabetic patients with PAD is essential to promptly start cardiovascular risk management (CVRM) and thus reduce the risk of events.[15] It is therefore crucial to have

a test that can reliably rule out PAD (i.e. have a low NLR). In this way, the diagnosis is less likely to be missed and more patients will be referred for additional imaging, CVRM, and timely revascularization if necessary. Although this would be the most optimal scenario, it is contrary to currently used tests, in which a high PLR and suboptimal NLR is generally seen.

This systematic review has several limitations. First, the overall methodological quality of the included studies was low. Risk of bias or a concern regarding applicability was present in 20 of the 23 included studies. The QUADAS 2-tool showed a notably high risk of bias regarding patient selection. Additionally, sample sizes were small; in 10 of the included studies less than 100 patients were included. Secondly, the heterogeneity in results was high, with wide ranging PLR and NLR values. Thirdly, data presentation was not uniform across studies exploring a specific technique, and many studies showed a wide variation in index test thresholds. Finally, performing a meta-analysis of the data presented in this review was not possible due to both clinical and methodological heterogeneity. Clinical variation was present due to heterogeneous patient groups (DM versus CKD, infection, age), bedside tests (with corresponding cut-off values and way of measurement), reference test (method and percentage of stenosis defined as PAD) and different exclusion criteria across the studies. Methodological heterogeneity was also present, and included study design (prospective vs. retrospective) and risk of bias (blinding of study). We thus advise tentative interpretation of the results presented in this review, and emphasize the need for standardized research using the QUADAS 2-tool[26] to establish clinical applicability. Also, future (prospective) studies should focus on ruling out PAD, with emphasis on a homogeneous patient group in which all patients receive the same reference test.

Conclusion

Overall, it remains challenging to rule in or rule out PAD in patients prone to MAC. Based on the results of this systematic review, we counsel against the use of a single bedside test. The ABI (<0·9 and exclusion of >1·3) seems useful to diagnose PAD, and CWD (loss of triphasic pattern) was accurate to rule out PAD. However, the included studies must be interpreted with caution due to serious concerns pertaining to the reliability of these studies and thereby the clinical applicability of the bedside tests explored. Not only more methodologically well-designed studies should be performed, but alternative bedside tests must also be investigated to improve the diagnostic accuracy in patients with MAC.

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Search strategy

In cooperation with a trained librarian (JS), a detailed search strategy was composed. The following databases were searched: PubMed, Embase (OVID-version), Web of Science, Cochrane Library, and Emcare. The query consisted of the combination of the following concepts:

- Peripheral arterial diseases, including DM and CKD
- Bedside non-invasive diagnostic tests (e.g., ABI, TP, TBI)
- Imaging techniques (reference standard)

These concepts were combined using six search strands in order to maximize relevancy and minimize noise. For the different concepts, all relevant keyword variations were used, not only keyword variations in the controlled vocabularies of the various databases, but the free text word variations of these concepts as well. The search strategy was optimized for all consulted databases, taking into account the differences of the various controlled vocabularies as well as the differences of database-specific technical variations (e.g., the use of quotation marks). The search was limited to English language articles. The final search was performed on February 10th, 2021. The bibliographic databases yielded 1016 regular references and 164 meeting abstract references. Full details of the search strategy can be found in Supplement S1.

Supplement S1: Search strategy details

Database	Search Strategy	Number of references	Number of unique references
PubMed	((("Peripheral Arterial Disease"[majr] OR "Peripheral Arterial Disease"[ti] OR "Peripheral Arterial Diseases"[ti] OR "Peripheral Artery Disease"[ti] OR "Peripheral Artery Diseases"[ti] OR "PAD"[ti] OR "peripheral arterial occlusive disease"[ti] OR "peripheral arterial occlusive diseases"[ti] OR "peripheral artery occlusive disease"[ti] OR "peripheral artery occlusive diseases"[ti] OR "Peripheral Vascular Diseases"[majr:noexp] OR "Peripheral Angiopathies"[ti] OR "Peripheral Angiopathy"[ti] OR "Peripheral Arteriopathies"[ti] OR "Peripheral Arteriopathy"[ti] OR "Peripheral Vasculopathies"[ti] OR "Peripheral Vasculopathy"[ti] OR "Monckeberg Medial Calcific Sclerosis"[majr] OR "Monckeberg's Medial Calcific Sclerosis"[ti] OR "Monckeberg's Sclerosis"[ti] OR "Monckeberg Sclerosis"[ti] OR "Mönckebergs Sclerosis"[ti] OR "Mönckeberg's Medial Calcific Sclerosis"[ti] OR "Mönckeberg's Sclerosis"[ti] OR "Mönckeberg Sclerosis"[ti] OR "Mönckebergs Sclerosis"[ti] OR "Monckeberg"[ti] OR "Monckeberg*"[ti] OR "Moenckeberg"[ti] OR "Moenckeberg*"[ti] OR "Medial Calcific Sclerosis"[ti] OR "Medial Calcific Scleroses"[ti] OR "Mönckeberg Medial Calcific Sclerosis"[ti] OR "incompressible arter*"[ti] OR "incompressible vessel*"[ti] OR "medial calcified arter*"[ti] OR (("Arterial Occlusive Diseases"[majr] OR "Peripheral Vascular Diseases"[majr]) AND ("peripheral"[ti] OR "peripheral*"[ti] OR "limbs"[ti] OR "limb"[ti] OR "leg"[ti] OR "legs"[ti] OR "extremity"[ti] OR "extremities"[ti] OR "arm"[ti] OR "arms"[ti])) OR "Intermittent Claudication"[majr] OR "Intermittent Claudication"[ti] OR "Leriche Syndrome"[majr] OR "Leriche Syndrome"[ti] OR "Leriche's Syndrome"[ti] OR "Leriches Syndrome"[ti] OR "Arteriosclerosis Obliterans"[majr] OR "Arteriosclerosis Obliterans"[ti] OR (("Atherosclerosis"[majr] OR "Arteriosclerosis"[majr] OR "Atherosclerosis"[ti] OR "Arteriosclerosis"[ti]) AND ("peripheral"[ti] OR "peripheral*"[ti] OR "limbs"[ti] OR "limb"[ti] OR "leg"[ti] OR "legs"[ti] OR 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"Doppler wave form"[ti] OR "Doppler wave forms"[ti] OR "Ultrasonography, Doppler, Pulsed"[majr:noexp] OR "Pulsed Doppler"[ti] OR "Doppler Pulsed"[ti] OR "non-invasive"[ti] OR "non-invasiv*"[ti] OR "point-of-care test"[ti] OR "point-of-care tests"[ti]) AND ("Angiography"[majr] OR "Angiography"[ti] OR "Angiographies"[ti] OR "Angiogram"[ti] OR "Angiograms"[ti] OR "Angiogra*"[ti] OR "Arteriography"[ti] OR "Arteriographies"[ti] OR "Arteriogra*"[ti] OR "Angiography, Digital Subtraction"[majr] OR "Digital Subtraction Angiography"[ti] OR "DSA"[ti] OR "Magnetic Resonance Angiography"[majr] OR "MRI Angiography"[ti] OR "MRI Angiographies"[ti] OR "Magnetic Resonance Angiography"[ti] OR "Magnetic Resonance Angiographies"[ti] OR "MRA"[ti] OR "Perfusion Magnetic Resonance Imaging"[ti] OR "Perfusion Weighted MRI"[ti] OR "Computed Tomography Angiography"[majr] OR "Computed Tomography Angiography"[ti] OR "Computed Tomography Angiographies"[ti] OR "CT Angiography"[ti] OR "CT Angiographies"[ti] OR 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"Prospective Studies"[mesh] OR "Retrospective Studies"[mesh] OR "Cohort"[tiab] OR "Cohorts"[tiab] OR "Follow-Up"[tiab] OR "Longitudinal"[tiab] OR "Prospective"[tiab] OR "Retrospective"[tiab] OR "Cross-Sectional Studies"[mesh] OR "Cross-Sectional"[tiab] OR "Observational Study"[pt] OR "Observational Studies as Topic"[mesh] OR "Observational Study"[tiab] OR "effectiveness"[tiab] OR "efficacy"[tiab])) OR (("Peripheral Arterial Disease"[majr] OR "Peripheral Arterial Disease"[ti] OR "Peripheral Arterial Diseases"[ti] OR "Peripheral Artery Disease"[ti] OR "Peripheral Artery Diseases"[ti] OR "PAD"[ti] OR "peripheral arterial occlusive disease"[ti] OR "peripheral arterial occlusive diseases"[ti] OR "peripheral artery occlusive disease"[ti] OR "peripheral artery occlusive diseases"[ti] OR "Peripheral Vascular Diseases"[majr:noexp] OR "Peripheral Angiopathies"[ti] OR "Peripheral Angiopathy"[ti] OR "Peripheral Arteriopathies"[ti] OR "Peripheral Arteriopathy"[ti] OR "Peripheral Vasculopathies"[ti] OR "Peripheral Vasculopathy"[ti] OR "Monckeberg Medial Calcific Sclerosis"[majr] OR "Monckeberg's Medial Calcific Sclerosis"[ti] OR "Monckeberg's Sclerosis"[ti] OR "Monckeberg Sclerosis"[ti] OR "Monckebergs Sclerosis"[ti] OR "Mönckeberg's Medial Calcific Sclerosis"[ti] OR "Mönckeberg's Sclerosis"[ti] OR "Mönckeberg Sclerosis"[ti] OR "Mönckebergs Sclerosis"[ti] OR "Monckeberg"[ti] OR "Monckeberg*"[ti] OR "Moenckeberg"[ti] OR "Moenckeberg*"[ti] OR "Medial Calcific Sclerosis"[ti] OR "Medial Calcific Scleroses"[ti] OR "Mönckeberg Medial Calcific Sclerosis"[ti] OR "incompressible arter*"[ti] OR "incompressible vessel*"[ti] OR "medial calcified arter*"[ti] OR (("Arterial Occlusive Diseases"[majr] OR "Peripheral Vascular Diseases"[majr]) AND ("peripheral"[ti] OR "peripheral*"[ti] OR "limbs"[ti] OR "limb"[ti] OR "leg"[ti] OR "legs"[ti] OR "extremity"[ti] OR "extremities"[ti] OR "arm"[ti] OR "arms"[ti])) OR "Intermittent Claudication"[majr] OR "Intermittent Claudication"[ti] OR "Leriche 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Oximetries"[ti] OR "Pulse Oximetry"[ti] OR "transcutaneous oxygen tension"[ti] OR "transcutaneous oxygen"[ti] OR "Pulse"[majr] OR "Pulse*"[ti] OR "pulsation"[ti] OR "pulsations"[ti] OR "Blood Gas Monitoring, Transcutaneous"[majr] OR "Transcutaneous Blood Gas	711	711

Database	Search Strategy	Number of references	Number of unique references
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"effectiveness"[tiab] OR "efficacy"[tiab]) OR (("Peripheral Arterial Disease"[majr] OR "Peripheral Arterial Disease"[ti] OR "Peripheral Arterial Diseases"[ti] OR "Peripheral Artery Disease"[ti] OR "Peripheral Artery Diseases"[ti] OR "PAD"[ti] OR "peripheral arterial occlusive disease"[ti] OR "peripheral arterial occlusive diseases"[ti] OR "peripheral artery occlusive disease"[ti] OR "peripheral artery occlusive diseases"[ti] OR "Peripheral Vascular Diseases"[majr:noexp] OR "Peripheral Angiopathies"[ti] OR "Peripheral Angiopathy"[ti] OR "Peripheral Arteriopathies"[ti] OR "Peripheral Arteriopathy"[ti] OR "Peripheral Vasculopathies"[ti] OR "Peripheral Vasculopathy"[ti] OR "Monckeberg Medial Calcific Sclerosis"[majr] OR "Monckeberg's Medial Calcific Sclerosis"[ti] OR "Monckeberg's Sclerosis"[ti] OR "Monckeberg Sclerosis"[ti] OR "Monckebergs Sclerosis"[ti] OR "Mönckeberg's Medial Calcific Sclerosis"[ti] OR "Mönckeberg's Sclerosis"[ti] OR "Mönckeberg Sclerosis"[ti] OR "Mönckebergs 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OR "leg"[ti] OR "legs"[ti] OR "extremity"[ti] OR "extremities"[ti] OR "arm"[ti] OR "arms"[ti]))) AND ("Ankle Brachial Index"[majr] OR "Ankle Brachial Indices"[ti] OR "Ankle-Brachial Index"[ti] OR "Ankle-Brachial Indices"[ti] OR "anklebrachial index"[ti] OR "anklebrachialindex"[ti] OR "ankle brachial"[ti] OR "anklebrachial"[ti] OR "ABI"[ti] OR "Toe Brachial Index"[ti] OR "Toe Brachial Indices"[ti] OR "Toe-Brachial Index"[ti] OR "Toe-Brachial Indices"[ti] OR "Toe Pressure"[ti] OR "toe brachial"[ti] OR "toebrachial"[ti] OR "TBI"[ti] OR "TP"[ti] OR "Oximetry"[majr] OR "Oximetry"[ti] OR "Oximetries"[ti] OR "Oximetr*"[ti] OR "Pulse Oximetries"[ti] OR "Pulse Oximetry"[ti] OR "transcutaneous oxygen tension"[ti] OR "transcutaneous oxygen"[ti] OR "Pulse"[majr] OR "Pulse*"[ti] OR "pulsation"[ti] OR "pulsations"[ti] OR "Blood Gas Monitoring, Transcutaneous"[majr] OR "Transcutaneous Blood Gas Monitoring"[ti] OR "Transcutaneous Capnometry"[ti] OR "PtcO2"[ti] OR "TcPCO2"[ti] OR "Doppler waveform"[ti] OR "Doppler waveforms"[ti] OR "Doppler wave form"[ti] OR "Doppler wave forms"[ti] OR "Ultrasonography, Doppler, Pulsed"[majr:noexp] OR "Pulsed Doppler"[ti] OR "Doppler Pulsed"[ti] OR "non-invasive"[ti] OR "non-invasiv*"[ti] OR "point-of-care test"[ti] OR "point-of-care tests"[ti] OR "point-of-care test"[ti] OR "point-of-care tests"[ti]) AND ("Angiography"[majr] OR "Angiography"[ti] OR "Angiographies"[ti] OR "Angiogram"[ti] OR "Angiograms"[ti] OR "Angiogra*"[ti] OR "Arteriography"[ti] OR "Arteriographies"[ti] OR "Arteriogra*"[ti] OR "Angiography, Digital Subtraction"[majr] OR "Digital Subtraction Angiography"[ti] OR "DSA"[ti] OR "Magnetic Resonance Angiography"[majr] OR "MRI Angiography"[ti] OR "MRI Angiographies"[ti] OR "Magnetic Resonance Angiography"[ti] OR "Magnetic Resonance Angiographies"[ti] OR "MRA"[ti] OR "Perfusion Magnetic Resonance Imaging"[ti] OR "Perfusion Weighted MRI"[ti] OR "Computed Tomography Angiography"[majr] OR "Computed Tomography Angiography"[ti] OR "Computed Tomography Angiographies"[ti] OR "CT Angiography"[ti] OR "CT Angiographies"[ti] OR "CTA"[ti] OR "Ultrasonography, Doppler, Duplex"[majr:noexp] OR "Duplex Doppler"[ti] OR "Doppler Duplex"[ti] OR "Ultrasonography, Doppler, Color"[majr:noexp] OR "Doppler Color"[ti] OR "Color Doppler"[ti] OR "Doppler Colour"[ti] OR "Colour Doppler"[ti] OR "color duplex"[ti] OR "colour duplex"[ti] OR "Laser-Doppler Flowmetry"[majr] OR "duplex color"[ti] OR "duplex colour"[ti] OR "CDUS»[ti] OR "Plethysmography"[majr] OR "Plethysmography"[ti] OR "Plethysmogra*"[ti] OR "color spectral waveforms"[ti] OR "color spectral waveform"[ti] OR "color spectral wave forms"[ti] OR "color spectral wave form"[ti] OR "colour spectral waveforms"[ti] OR "colour spectral waveform"[ti] OR "colour spectral wave forms"[ti] OR "colour spectral wave form"[ti] OR "Peripheral Vascular Diseases/diagnostic imaging"[majr:noexp] OR "Comparative Study"[pt]) AND ("Monckeberg Medial Calcific Sclerosis"[Mesh] OR "Monckeberg's Medial Calcific Sclerosis"[tw] OR "Monckeberg's Sclerosis"[tw] OR "Monckeberg Sclerosis"[tw] OR "Monckebergs Sclerosis"[tw] OR "Mönckeberg's Medial Calcific Sclerosis"[tw] OR "Mönckeberg's Sclerosis"[tw] OR "Mönckeberg Sclerosis"[tw] OR "Mönckebergs Sclerosis"[tw] OR "Monckeberg"[tw] OR "Monckeberg*"[tw] OR "Moenckeberg"[tw] OR "Moenckeberg*"[tw] OR "Medial Calcific Sclerosis"[tw] OR "Medial Calcific Scleroses"[tw] OR "Mönckeberg Medial Calcific Sclerosis"[tw] OR "incompressible arter*"[tw] OR "incompressible vessel*"[tw] OR "medial calcified arter*"[tw] OR "media sclerosis"[tw] OR "mediasclerosis"[tw] OR "in-compressible artery"[tw] OR "incompressible artery"[tw] OR "in-compressible arteries"[tw] OR "incompressible arteries"[tw] OR "in-compressible vessel"[tw] OR "incompressible vessel"[tw] OR "in-compressible vessels"[tw] OR "incompressible vessels"[tw] OR "non-compressible artery"[tw] OR "noncompressible artery"[tw] OR "non-compressible arteries"[tw] OR "noncompressible arteries"[tw] OR 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Database	Search Strategy	Number of references	Number of unique references
PubMed	vessel*"[ti] OR "medial calcified arter*"[ti] OR (("Arterial Occlusive Diseases"[majr] OR "Peripheral Vascular Diseases"[majr]) AND ("peripheral"[ti] OR "peripheral*"[ti] OR "limbs"[ti] OR "limb"[ti] OR "leg"[ti] OR "legs"[ti] OR "extremity"[ti] OR "extremities"[ti] OR "arm"[ti] OR "arms"[ti])) OR "Intermittent Claudication"[majr] OR "Intermittent Claudication"[ti] OR "Leriche Syndrome"[majr] OR "Leriche Syndrome"[ti] OR "Leriche's Syndrome"[ti] OR "Leriches Syndrome"[ti] OR "Arteriosclerosis Obliterans"[majr] OR "Arteriosclerosis Obliterans"[ti] OR (("Atherosclerosis"[majr] OR "Arteriosclerosis"[majr] OR "Atherosclerosis"[ti] OR "Arteriosclerosis"[ti]) AND ("peripheral"[ti] OR "peripheral*"[ti] OR "limbs"[ti] OR "limb"[ti] OR "leg"[ti] OR "legs"[ti] OR "extremity"[ti] OR "extremities"[ti] OR "arm"[ti] OR "arms"[ti]))) AND ("clinical test"[ti] OR "clinical tests"[ti] OR "screening test"[ti] OR "screening tests"[ti] OR "point-of-care test"[ti] OR "point-of-care tests"[ti])) OR 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"Ultrasonography, Doppler, Pulsed"[majr:noexp] OR "Pulsed Doppler"[ti] OR "Doppler Pulsed"[ti] OR "non-invasive"[ti] OR "non-invasiv*"[ti] OR "point-of-care test"[ti] OR "point-of-care tests"[ti]) AND ("Angiography"[majr] OR "Angiography"[ti] OR "Angiographies"[ti] OR "Angiogram"[ti] OR "Angiograms"[ti] OR "Angiogra*"[ti] OR "Arteriography"[ti] OR "Arteriographies"[ti] OR "Arteriogra*"[ti] OR "Angiography, Digital Subtraction"[majr] OR "Digital Subtraction Angiography"[ti] OR "DSA"[ti] OR "Magnetic Resonance Angiography"[majr] OR "MRI Angiography"[ti] OR "MRI Angiographies"[ti] OR "Magnetic Resonance Angiography"[ti] OR "Magnetic Resonance Angiographies"[ti] OR "MRA"[ti] OR "Perfusion Magnetic Resonance Imaging"[ti] OR "Perfusion Weighted MRI"[ti] OR "Computed Tomography Angiography"[majr] OR "Computed Tomography Angiography"[ti] OR "Computed Tomography Angiographies"[ti] OR "CT Angiography"[ti] OR "CT Angiographies"[ti] OR "CTA"[ti] OR "Ultrasonography, Doppler, Duplex"[majr:noexp] OR 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test"[tiab] OR "point-of-care tests"[tiab]) AND ("Angiography"[mesh] OR "Angiography"[tiab] OR		

Database	Search Strategy	Number of references	Number of unique references
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*"pulsed Doppler echocardiography"/ OR "Pulsed Doppler".ti,ab OR "Doppler Pulsed".ti,ab OR "non-invasive".ti,ab OR "non-invasiv*".ti,ab OR "point-of-care test".ti,ab OR "point-of-care tests".ti,ab OR "point-of-care test".ti,ab OR "point-of-care tests".ti,ab) AND (exp *"Angiography"/ OR "Angiography".ti,ab OR "Angiographies".ti,ab OR "Angiogram".ti,ab OR "Angiograms".ti,ab OR			

Database	Search Strategy	Number of references	Number of unique references
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Web of Science	((ti=("Peripheral Occlusive Arterial Disease" OR "Peripheral Arterial Disease" OR "Peripheral Arterial Diseases" OR "Peripheral Artery Disease" OR "Peripheral Artery Diseases" OR "PAD" OR "peripheral arterial occlusive disease" OR "peripheral arterial occlusive diseases" OR "peripheral artery occlusive disease" OR "peripheral artery occlusive diseases" OR "Peripheral Vascular Disease" OR "Peripheral Angiopathies" OR "Peripheral Angiopathy" OR "Peripheral Arteriopathies" OR "Peripheral Arteriopathy" OR "Peripheral Vasculopathies" OR "Peripheral Vasculopathy" OR "Monckeberg Medial Calcific Sclerosis" OR "Monckeberg's Medial Calcific Sclerosis" OR "Monckeberg's Sclerosis" OR "Monckeberg Sclerosis" OR "Monckebergs Sclerosis" OR "Mönckeberg's Medial Calcific Sclerosis" OR "Mönckeberg's Sclerosis" OR "Mönckeberg Sclerosis" OR "Mönckebergs Sclerosis" OR "Monckeberg" OR "Monckeberg*" OR "Moenckeberg" OR "Moenckeberg*" OR "Medial Calcific Sclerosis" OR "Medial Calcific Scleroses" 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Angiographies" OR "Magnetic Resonance Angiography" OR "Magnetic Resonance Angiographies" OR "MRA" OR "perfusion weighted imaging" OR "Perfusion Magnetic Resonance Imaging" OR "Perfusion Weighted MRI" OR "Computed Tomographic Angiography" OR "Computed Tomography Angiography" OR "Computed Tomography Angiographies" OR "CT Angiography" OR "CT Angiographies" OR "CTA" OR "duplex Doppler ultrasonography" OR "Duplex Doppler" OR "Doppler Duplex" OR "color Doppler flowmetry" OR "Doppler Color" OR "Color Doppler" OR "Doppler Colour" OR "Colour Doppler" OR "color duplex" OR "colour duplex" OR "duplex color" OR "duplex colour" OR "CDUS» OR "Plethysmography" OR "Plethysmography" OR "Plethysmogra*" OR "color spectral waveforms" OR "color spectral waveform" OR "color spectral wave forms" OR "color spectral wave form" OR "colour spectral waveforms" OR "colour spectral waveform" OR "colour spectral wave forms" OR "colour spectral wave form") AND TS=("Sensitivity and Specificity" OR "Sensitivity" OR "Specificity" OR "Predictive Value" OR "ROC Curve" OR "Signal-To-Noise" OR "limit of detection" OR "Cohort Analysis" OR "Follow Up" OR "Longitudinal Study" OR "Prospective Study" OR "Retrospective Study" OR "Cohort" OR "Cohorts" OR "Follow-Up" OR "Longitudinal" OR "Prospective" OR "Retrospective" OR "Cross-Sectional Study" OR "Cross-Sectional" OR "Observational Study" OR "Observational Study" OR "effectiveness" OR "efficacy")) OR (ti=("Peripheral Occlusive Arterial Disease" OR "Peripheral Arterial Disease" OR "Peripheral Arterial Diseases" OR "Peripheral Artery Disease" OR "Peripheral Artery Diseases" OR "PAD" OR "peripheral arterial occlusive disease" OR "peripheral arterial occlusive diseases" OR "peripheral artery occlusive disease" OR "peripheral artery occlusive diseases" OR "Peripheral Vascular Disease" OR "Peripheral Angiopathies" OR "Peripheral Angiopathy" OR "Peripheral Arteriopathies" OR "Peripheral Arteriopathy" OR "Peripheral Vasculopathies" OR "Peripheral Vasculopathy" OR "Monckeberg Medial Calcific Sclerosis" OR "Monckeberg's Medial Calcific Sclerosis" OR "Monckeberg's Sclerosis" OR "Monckeberg Sclerosis" OR "Monckebergs Sclerosis" OR "Mönckeberg's Medial Calcific Sclerosis" OR "Mönckeberg's Sclerosis" OR "Mönckeberg Sclerosis" OR "Mönckebergs Sclerosis" OR "Monckeberg" OR "Monckeberg*" OR "Moenckeberg" OR "Moenckeberg*" OR "Medial Calcific Sclerosis" OR "Medial Calcific Scleroses" OR "Mönckeberg Medial Calcific Sclerosis" OR "incompressible arter*" OR "incompressible vessel*" OR "medial calcified arter*" OR (("Peripheral Occlusive Arterial Disease" OR "Peripheral Vascular Disease") AND ("peripheral" OR "peripheral*" OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms")) OR "Intermittent Claudication" OR "Intermittent Claudication" OR "Leriche Syndrome" OR "Leriche Syndrome" OR "Leriche's Syndrome" OR "Leriches Syndrome" OR "Arteriosclerosis Obliterans" OR (("Atherosclerosis" OR "Arteriosclerosis" OR "Atherosclerosis" OR "Arteriosclerosis") AND ("peripheral" OR "peripheral*" OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms"))) AND ti=("Ankle Brachial Index" OR "Ankle Brachial Indices" OR "Ankle-Brachial Index" OR "Ankle-Brachial Indices" OR "anklebrachial index" OR "anklebrachialindex" OR "ankle brachial" OR "anklebrachial" OR "ABI" OR "Toe Brachial Index" OR "Toe Brachial Indices" OR "Toe-Brachial Index" OR "Toe-Brachial Indices" OR "Toe Pressure" OR "toe brachial" OR "toebrachial" OR "TBI" OR "TP" OR "Oximetry" OR "Oximetry" OR "Oximetries" OR "Oximetr*" OR "Pulse Oximetries" OR "Pulse Oximetry" OR "transcutaneous oxygen tension" OR "transcutaneous oxygen" OR "Pulse" OR "Pulse*" OR "pulsation" OR "pulsations" OR	91 18 meeting abstracts	15 8 meeting abstracts

Database	Search Strategy	Number of references	Number of unique references
Web of Science	"Transcutaneous Oxygen Monitoring" OR "Transcutaneous Blood Gas Monitoring" OR "Transcutaneous Capnometry" OR "PtcO2" OR "TcPCO2" OR "Doppler waveform" OR "Doppler waveforms" OR "Doppler wave form" OR "Doppler wave forms" OR "pulsed Doppler echocardiography" OR "Pulsed Doppler" OR "Doppler Pulsed" OR "non-invasive" OR "non-invasiv*" OR "point-of-care test" OR "point-of-care tests") AND ti=("Sensitivity and Specificity" OR "Sensitivity" OR "Specificity" OR "Predictive Value" OR "ROC Curve" OR "Signal-To-Noise" OR "limit of detection" OR "Cohort Analysis" OR "Follow Up" OR "Longitudinal Study" OR "Prospective Study" OR "Retrospective Study" OR "Cohort" OR "Cohorts" OR "Follow-Up" OR "Longitudinal" OR "Prospective" OR "Retrospective" OR "Cross-Sectional Study" OR "Cross-Sectional" OR "Observational Study" OR "Observational Study" OR "effectiveness" OR "efficacy")) OR (ti=("Peripheral Occlusive Arterial Disease" OR "Peripheral Arterial Disease" OR "Peripheral Arterial Diseases" OR "Peripheral Artery Disease" OR "Peripheral Artery Diseases" OR "PAD" OR "peripheral arterial occlusive disease" OR "peripheral arterial occlusive diseases" OR "peripheral artery occlusive disease" OR "peripheral artery occlusive diseases" OR "Peripheral Vascular Disease" OR "Peripheral Angiopathies" OR "Peripheral Angiopathy" OR "Peripheral Arteriopathies" OR "Peripheral Arteriopathy" OR "Peripheral Vasculopathies" OR "Peripheral Vasculopathy" OR "Monckeberg Medial Calcific Sclerosis" OR "Monckeberg's Medial Calcific Sclerosis" OR "Monckeberg's Sclerosis" OR "Monckeberg Sclerosis" OR "Monckebergs Sclerosis" OR "Mönckeberg's Medial Calcific Sclerosis" OR "Mönckeberg's Sclerosis" OR "Mönckeberg Sclerosis" OR "Mönckebergs Sclerosis" OR "Monckeberg" OR "Monckeberg*" OR "Moenckeberg" OR "Moenckeberg*" OR "Medial Calcific Sclerosis" OR "Medial Calcific Scleroses" OR "Mönckeberg Medial Calcific Sclerosis" OR "incompressible arter*" OR "incompressible vessel*" OR "medial calcified arter*" OR (("Peripheral Occlusive Arterial Disease" OR "Peripheral Vascular Disease") AND ("peripheral" OR "peripheral*" OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities")) OR "Intermittent Claudication" OR "Intermittent Claudication" OR "Leriche Syndrome" OR "Leriche Syndrome" OR "Leriche's Syndrome" OR "Leriches Syndrome" OR "Arteriosclerosis Obliterans" OR (("Atherosclerosis" OR "Arteriosclerosis" OR "Atherosclerosis" OR "Arteriosclerosis") AND ("peripheral" OR "peripheral*" OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms"))) AND ti=("Ankle Brachial Index" OR "Ankle Brachial Indices" OR "Ankle-Brachial Index" OR "Ankle-Brachial Indices" OR "anklebrachial index" OR "anklebrachialindex" OR "ankle brachial" OR "anklebrachial" OR "ABI" OR "Toe Brachial Index" OR "Toe Brachial Indices" OR "Toe-Brachial Index" OR "Toe-Brachial Indices" OR "Toe Pressure" OR "toe brachial" OR "toebrachial" OR "TBI" OR "TP" OR "Oximetry" OR "Oximetry" OR "Oximetries" OR "Oximetr*" OR "Pulse Oximetries" OR "Pulse Oximetry" OR "transcutaneous oxygen tension" OR "transcutaneous oxygen" OR "Pulse" OR "Pulse*" OR "pulsation" OR "pulsations" OR "Transcutaneous Oxygen Monitoring" OR "Transcutaneous Blood Gas Monitoring" OR "Transcutaneous Capnometry" OR "PtcO2" OR "TcPCO2" OR "Doppler waveform" OR "Doppler waveforms" OR "Doppler wave form" OR "Doppler wave forms" OR "pulsed Doppler echocardiography" OR "Pulsed Doppler" OR "Doppler Pulsed" OR "non-invasive" OR "non-invasiv*" OR "point-of-care test" OR "point-of-care tests" OR "point-of-care test" OR "point-of-care tests" OR "point-of-care test" OR "point-of-care tests") AND ti=("Angiography" OR "Angiography" OR "Angiographies" OR "Angiogram" OR "Angiograms" OR "Angiogra*" OR "Arteriography" OR "Arteriographies" OR "Arteriogra*" OR "Digital Subtraction Angiography" OR "DSA" OR "Magnetic Resonance Angiography" OR "MRI Angiography" OR "MRI Angiographies" OR "Magnetic Resonance 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tests" OR "screening test" OR "screening tests" OR "point-of-care test" OR "point-of-care tests")) OR (ti=("Ankle Brachial Index" OR "Ankle Brachial Indices" OR "Ankle-Brachial Index" OR "Ankle-Brachial Indices" OR "anklebrachial index" OR "anklebrachialindex" OR "ankle brachial" OR "anklebrachial"		

Database	Search Strategy	Number of references	Number of unique references
Web of Science	OR "ABI" OR "Toe Brachial Index" OR "Toe Brachial Indices" OR "Toe-Brachial Index" OR "Toe-Brachial Indices" OR "Toe Pressure" OR "toe brachial" OR "toebrachial" OR "TBI" OR "TP" OR "Oximetry" OR "Oximetry" OR "Oximetries" OR "Oximetr*" OR "Pulse Oximetries" OR "Pulse Oximetry" OR "transcutaneous oxygen tension" OR "transcutaneous oxygen" OR "Pulse" OR "Pulse*" OR "pulsation" OR "pulsations" OR "Transcutaneous Oxygen Monitoring" OR "Transcutaneous Blood Gas Monitoring" OR "Transcutaneous Capnometry" OR "PtcO2" OR "TcPCO2" OR "Doppler waveform" OR "Doppler waveforms" OR "Doppler wave form" OR "Doppler wave forms" OR "pulsed Doppler echocardiography" OR "Pulsed Doppler" OR "Doppler Pulsed" OR "non-invasive" OR "non-invasiv*" OR "point-of-care test" OR "point-of-care tests" OR "point-of-care test" OR "point-of-care tests") AND ti=("Angiography" OR "Angiography" OR "Angiographies" OR "Angiogram" OR "Angiograms" OR "Angiogra*" OR "Arteriography" OR "Arteriographies" OR 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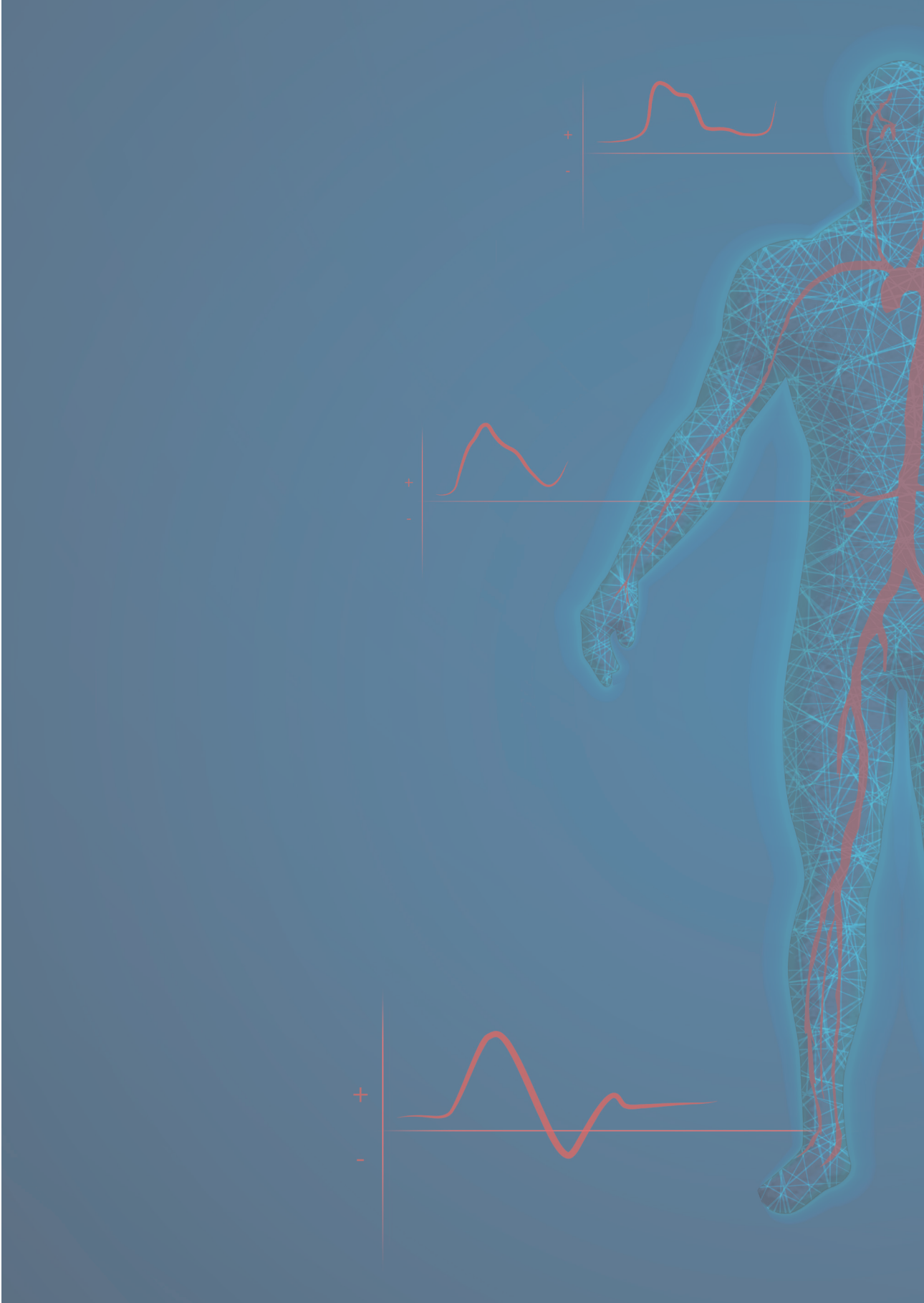
Chapter 3

Using maximal systolic acceleration to diagnose and assess the severity of peripheral artery disease in a flow model study

J Vasc Surg. 2020 Jan;71(1):242-249.

Jeroen J. W. M. Brouwers, Louk P. van Doorn, Rob C. van Wissen, Hein Putter, Jaap F. Hamming



Abstract

Background

Because of the presence of medial calcific sclerosis, both ankle-branchial index and toe pressure measures can yield misleading results when attempting to diagnose peripheral artery disease (PAD). A new ultrasound parameter, maximal systolic acceleration (ACC_{max}), can be an accurate tool for diagnosing PAD, including in diabetic patients. However, it has not been evaluated thoroughly. The aim of this study was to assess the feasibility of using ACC_{max} to diagnose and assess the severity of PAD.

Methods

The human circulatory system was simulated using an in vitro circulatory system driven by a pulsatile pneumatic pump. Arterial stenosis of various degrees (50%, 70%, 80%, and 90%) was simulated in order to investigate the change in several ultrasound parameters (including ACC_{max}), as well as the intraluminal mean arterial pressure gradient. In a separate set of measurements, interobserver variability was measured using two investigators who were unaware of the degree of stenosis.

Results

ACC_{max} significantly decreased ($P < .001$), and the pressure gradient increased ($P < .001$) as the degree of stenosis increased. Moreover, we found a strong correlation between ACC_{max} and the pressure gradient ($R^2 = 0.937$). Finally, interobserver variability with respect to ACC_{max} was extremely low, with an intraclass correlation coefficient of 0.99.

Conclusions

The results of this flow model study suggest that ACC_{max} can be a valid, noninvasive tool for diagnosing PAD. Moreover, our finding that ACC_{max} decreases as the severity of stenosis increases, together with the strong correlation between ACC_{max} and the pressure gradient, suggests that ACC_{max} may be useful as an alternative diagnostic tool for assessing the severity of PAD. These promising in vitro data warrant further study in a clinical setting.

Clinical Relevance

Limb pressure measurements and the determination of pressure index values (ankle-branchial index and toe pressure) are commonly used in patients with symptoms consistent with peripheral arterial disease. However, ankle-branchial index and toe pressure can be falsely elevated or falsely normal due to medial calcific sclerosis. In this in vitro flow-model study, the maximal systolic acceleration (ACC_{max}) significantly decreased as the degree of stenosis increased. Furthermore, there was a strong correlation between ACC_{max} and the intraluminal pressure gradient. These results suggest ACC_{max} may provide a robust noninvasive technique for assessing the severity of peripheral arterial disease.

Introduction

Several noninvasive tools are currently used for diagnosing and assessing the severity of atherosclerotic peripheral artery disease (PAD): ankle-branchial index (ABI), toe-brachial index (TBI), toe pressure (TP), and pulse volume recording.[1,2] Although an ABI value of <0.90 is considered a diagnostic criteria for PAD in patients with claudication,[3,4] the results of this test can be misleading as a result of vessel stiffness caused by medial calcific sclerosis, possibly leading to either a falsely high or falsely normal ankle pressure.[5] However, both TBI and TP are generally considered to be more reliable indicators of PAD severity in patients with incompressible crural and/or pedal arteries.[6] Yet, both TBI and TP can provide falsely elevated values as a result of incompressible digital arteries, and both tests are dependent on temperature.[7,8,9] Incompressible arteries occur primarily in patients with a long history of diabetes, advanced age, and/or end-stage renal disease. Compared to patients without diabetes, those with diabetes have a fourfold higher risk of developing PAD,[10] and 65% of patients with a diabetic foot ulcer also develop ischemic complications.[6,11] Furthermore, approximately 20% of patients with critical limb ischemia (CLI) have incompressible vessels due to artery calcification. Finally, the waveform morphology measured using pulse volume recording is relatively insensitive for diagnosing CLI.[12] Thus, determining the severity of PAD using currently available noninvasive measurements can be challenging, particularly in patients with CLI and/or diabetes.

A new noninvasive approach that is particularly promising for detecting and quantifying PAD is duplex-derived maximal systolic acceleration (ACC_{max}). Van Tongeren et al[13] and Buschmann et al[14] showed the accurate diagnostic properties of ACC_{max}, also in diabetic patients. Although ACC_{max} has already been used to detect renal artery stenosis,[15,16,17,18] to our knowledge, it has not been evaluated thoroughly for PAD. We think that if you want to introduce a new parameter to diagnose PAD, you must start from basic principles. Apart from complex clinical settings that occur in reality (eg, impact from cardiac output, shear rate, collateral circulation, vascular compliance, outflow obstruction), this in vitro flow model study investigated the impact of different artificial stenosis and compared ultrasound parameters with the intraluminal pressure gradient. From here, further structured substantiation of the ACC_{max} and its clinical value need to be determined.

Methods

In vitro circulatory system

Our in vitro circulatory system was previously validated with respect to simulating the human circulatory system.[19,20,21,22] Fig 1 shows a systematic representation of the in vitro circulatory system, which consists of a pneumatically driven pulsatile pump, a ball valve, a compliance air chamber, an arterial stenosis model (a removable tube for inserting the stenosis), a pressure band to simulate peripheral resistance, and a collateral system with intrinsic peripheral resistance. The following degrees of stenosis were used at two different lengths (2 and 8 cm): 50%, 70%, 80%, and 90%; these stenosis models were easily switched in the arterial stenosis model. Collateral peripheral resistance (Fig 1; F_{col}) was necessary in order to maintain consistent prestenotic mean arterial pressure (MAP) with the various setups. To investigate the correlation between Doppler ultrasound parameters with the degree of stenosis and intra-arterial pressure gradient, the other variables of the in vitro circulatory system, with regard to the peripheral resistance (distal to the stenosis; Fig 1, *F*), compliance, shear rate, and cardiac output, were unchanged during the different test setups. In addition, the pneumatically driven pulsatile pump settings used for the in vitro

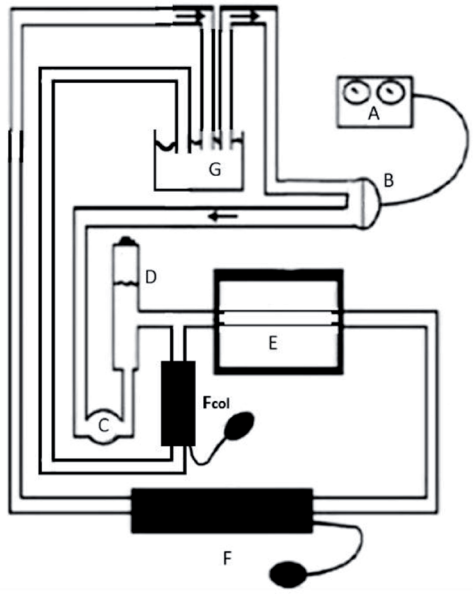


Fig 1: Schematic illustration depicting in vitro circulatory system used in this study. In vitro circulatory system was composed of (A) pneumatically driven pulsatile pump, (B) simulated left ventricle, (C) ball valve, (D) compliance air chamber, (E) arterial stenosis model, (F) pressure band to simulate peripheral resistance, (Fcol) collateral system with intrinsic peripheral resistance, and (G) open reservoir.

circulatory system were unchanged throughout the various measurements. The Doppler ultrasound parameters were measured 30 cm from the stenosis. To simulate human blood, a starch solution with the same viscosity as human blood was used.[19,21,22] SonoVue (Bracco Imaging Europe, Amsterdam, the Netherlands) was used to optimize the Doppler imaging wave.[23] Intraluminal prestenotic and poststenotic MAP was measured using a RadiAnalyzer Xpress device equipped with a PressureWire (St Jude Medical, St Paul, MN).

Test setups

Fig 2 shows an overview of the various setups used in this study. In setup 1, no stenosis is included. Setups 2 through 5 have various degrees of stenosis (2 cm). Setups 6 through 9 have various degrees of stenosis (8 cm). Finally, setups 10 through 13 have three 2-cm stenoses in series.

Degree of stenosis

In this study, each stenosis was concentric with the vessel, and the degree of stenosis was based on the reduction in the vessel's diameter. It is important to note that a reduction in

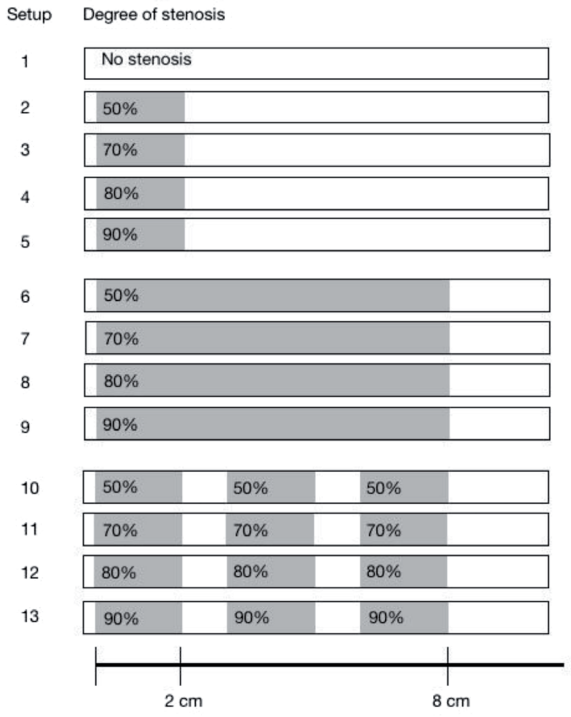


Fig 2: Schematic overview of various study setups. In setups 2 through 13, each stenosis (either 2 or 8 cm) is indicated in gray, with corresponding degree indicated as percentage.

diameter does not correlate with the same reduction in the cross-sectional area; for example, a 50% reduction in diameter corresponds to a 75% reduction in area.[24] Table I provides a summary of the stenoses used in this study and their corresponding reductions in diameter and area.

Degree of stenosis in diameter reduction	Diameter of stenosis, mm	Degree of stenosis in area reduction	Area of stenosis, mm^2
0	12.1	0	115.0
50%	6.1	75%	28.7
70%	3.6	91%	10.3
80%	2.4	96%	4.6
90%	1.2	99%	1.1

Table 1: Degree of stenosis and corresponding reduction in diameter and area of various stenoses

Doppler ultrasound

All Doppler ultrasound procedures were performed by the same vascular ultrasound specialist, who used an Acuson S2000 System, Helix Evolution (Siemens Medical Solutions, Ultrasound Division, Issaquah, Wash) equipped with a 9L4 9-4 MHz linear transducer. All measurements were performed with a fixed 60-degree angle of insonation. ACC_{max} was calculated by computer at a single representative curve as described by van Tongeren et al[13] and is expressed in meters per second. It is important to note that the ACC_{max} occurs at the maximal slope in the systolic phase (Fig 3). ACC_{max} was measured distal to the stenosis, so there is no interference from medial calcific sclerosis. ACC_{max} should not be confused with either acceleration time (AT) or mean systolic acceleration (ACC_{sys}).

Interobserver variability

In a separate set of measurements, interobserver variability of ACC_{max} was calculated using measurements obtained by two investigators who were unaware of the degree of stenosis. In this subset, only a single stenosis (50%, 70%, 80%, 90%, or no stenosis) was used in each experiment. For each degree of stenosis, ACC_{max} was measured five times by each investigator.

Distance between stenosis and measurement point

To examine the effect of the distance between the stenosis and ACC_{max}, ACC_{max} was measured at a distance of 30 and 20 cm from the stenosis in a test setup with an 80% stenosis and without stenosis.

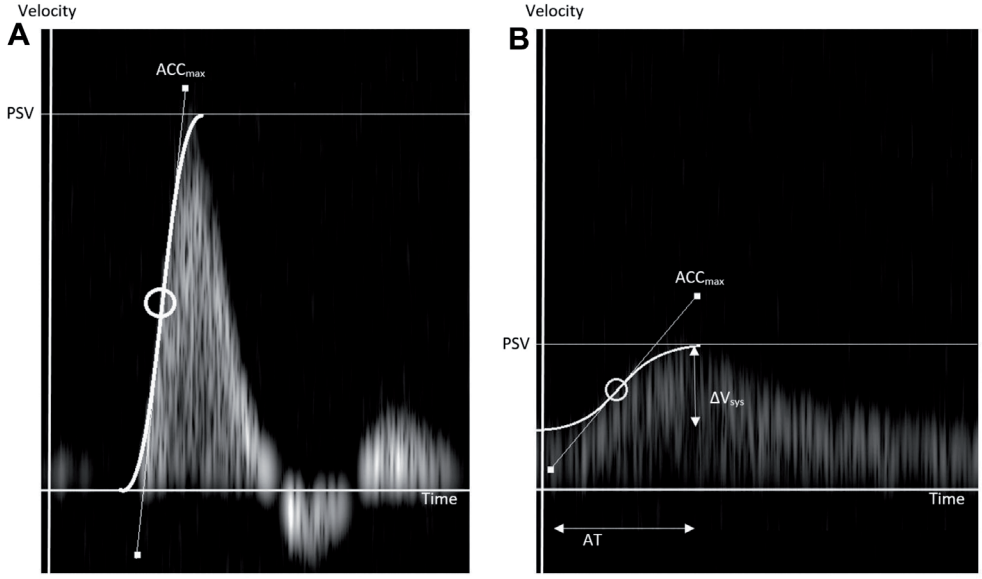


Fig 3: Example analysis of Doppler spectrum. A, Normal triphasic Doppler waveform. Maximal systolic acceleration (*ACCmax*) is measured at inflection point at which upstroke changes from concave up to concave down. It is equal to slope of tangent line on curve at inflection point. B, Example of abnormal monophasic Doppler waveform. ACC_{max}, peak systolic velocity (*PSV*), acceleration time (*AT*), and systolic velocity gradient (ΔV_{sys}) are shown. ACC_{max} is measured at visually judged maximum derivative of systolic phase. ACC_{max} should not be confused with mean systolic acceleration (ACC_{sys}), which is slope between beginning of systolic upstroke and peak of systole and is calculated using following equation: $ACC_{sys} = \Delta V_{sys}/AT$.

Statistical analysis

All analyses were conducted by SPSS Statistics 23.0 software (IBM, Armonk, NY). Linear regression was used to relate ACC_{max} to other ultrasound parameters and degree of stenosis. Differences with $P < .05$ were considered statistically significant. Using a linear regression model, a coefficient of determination (R^2) was used to determine the putative association between ultrasound parameters and the intraluminal MAP gradient. Interobserver variability was measured by calculating the intraclass correlation coefficient (ICC; two-way mixed, absolute agreement), which is a measure used to determine the consistency of repeated measures. Two separate investigators measured ACC_{max} with various degrees of stenosis; an ICC value of >0.9 indicates excellent agreement between the two investigators. An independent Student *t* test was used to investigate the effect of whether ACC_{max} was affected by the distance between the stenosis and the measurement points.

Results

In vitro circulatory system

In our in vitro circulatory system, intraluminal MAP was 90 mm Hg, and ACC_{max} was 9.17 m/s^2 without a stenosis (setup 1). With different setups, prestenotic pressure was consistent and ranged from 89 to 92 mm Hg.

ACC_{max} at various degrees of stenosis

Table II summarizes the measurements obtained with each setup. With increasing degrees of stenosis, ACC_{max} significantly decreased ($P < .001$) and the intraluminal pressure gradient significantly increased ($P < .001$).

Our analysis revealed a high coefficient of determination ($R^2 = 0.937$) for the association between ACC_{max} and the pressure gradient over all 13 setups. Table III summarizes the *P* values for the ultrasound parameters between the degree in stenosis and the association with the intraluminal pressure gradient. Overall, a high pressure gradient corresponded to a low ACC_{max} value (Fig 4).

Setup No.	Degree of stenosis, %	Length of stenosis, cm	$ACC_{max,}$ m/s^2	AT, seconds	$ACC_{sys,}$ m/s^2	PSV, cm/s	Pressure gradient, mm Hg
1	0	0	9.17	0.26	6.53	188	0
2	50	2	6.33	0.26	5.24	196	27
3	70	2	1.72	0.22	1.3	65	50
4	80	2	0.99	0.19	0.71	42	62
5	90	2	0.37	0.14	0.33	20	78
6	50	8	5.01	0.27	5.21	171	35
7	70	8	1.41	0.24	1.25	23	57
8	80	8	0.83	0.18	0.67	30	68
9	90	8	0.32	0.12	0.29	15	81
10	50	3 × 2	4.96	0.24	3.46	135	42
11	70	3 × 2	1.38	0.21	1.24	58	66
12	80	3 × 2	0.44	0.17	0.41	25	71
13	90	3 × 2	0.13	0.19	0.12	12	83

Table 2: Summary of ultrasound parameters and intraluminal mean arterial pressure gradients
ACC_{max}, Maximal systolic acceleration; *ACC_{sys}*, mean systolic acceleration; *AT,* acceleration time; *PSV,* peak systolic velocity.

Ultrasound parameter	*P* value between degrees of stenosis	R^2 with pressure gradient
ACC_{max}, m/s²	<.001	0.937
AT, seconds	.031	0.696
ACC_{sys}, m/s²	<.001	0.904
PSV, cm/s	.001	0.845

Table 3: Summary of analysis of various ultrasound parameters between different test setups
ACC_{max}, Maximal systolic acceleration; ACC_{sys}, mean systolic acceleration; *AT,* acceleration time; *PSV,* peak systolic velocity.
P values are provided for association of ultrasound parameter between different degrees of stenosis; there is a significance difference in ACC_{max} ($P < .001$) between different degree of stenosis: no stenosis (test setup 1), 50% (test setup 2, 6, and 10), 70% (test setup 3, 7, and 11), 80% (test setup 4, 8, and 12), and 90% (test setup 5, 9, and 13). Coefficients of determination (R^2) between each ultrasound parameter and pressure gradient (over all test setups) are shown.

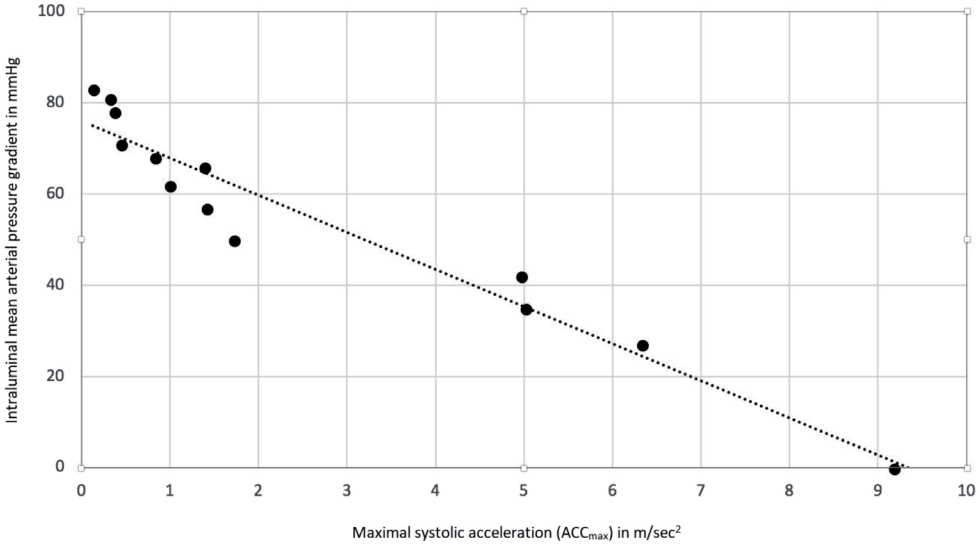


Fig 4: Intraluminal mean arterial pressure plotted against maximal systolic acceleration (*ACCmax*); coefficient of determination (R^2) was 0.937, showing high correlation. Regression line added.

In Fig 5, we plotted ACC_{max} and the intraluminal pressure gradient against the various degrees of stenosis and setups. With respect to both ACC_{max} and the pressure gradient, the setup with three 2-cm stenoses (setup 13; Fig 2) had the highest impact, and each 8-cm stenosis had a higher impact compared to the corresponding 2-cm stenosis. However, no significant differences in ACC_{max} and pressure gradient were found between 2-cm, 8-cm, and three 2-cm stenoses.

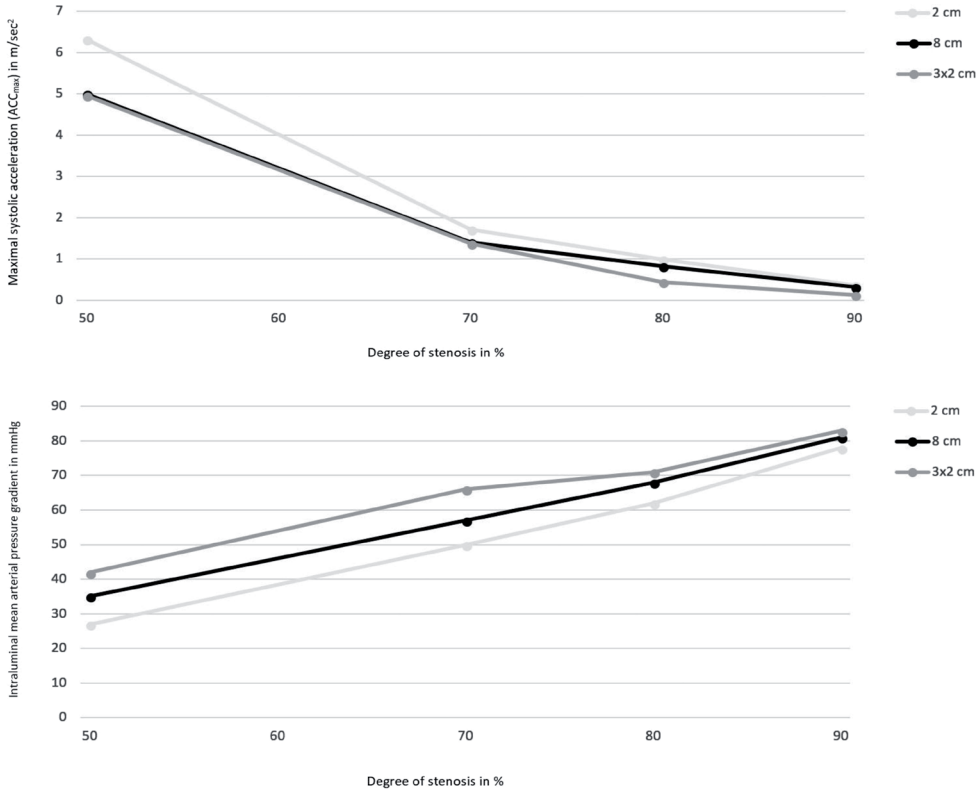


Fig 5: Maximal systolic acceleration (*ACCmax*; *top*) and intraluminal pressure gradient (*bottom*) are plotted against various degrees of stenosis based on reduction in diameter.

Interobserver variability

Two separate investigators who were unaware of the degree of stenosis measured ACC_{max}. Our analysis revealed that the ICC was 0.99 between the two investigators with respect to measuring ACC_{max} at various degrees of stenosis.

Distance between stenosis and measurement point

Finally, to examine whether ACC_{max} was affected by the distance between the stenosis and the measurement point, we measured ACC_{max} at 30 cm and 20 cm from the point of 80% stenosis and in setup 1 (Fig 2; ie, without stenosis). We found no significant differences in ACC_{max} between a distance of 30 cm and a distance of 20 cm with 80% stenosis ($P = .26$) and between the same two distances without stenosis ($P = .66$).

Discussion

ACC_{max} can be measured accurately with low interobserver variability in an experimental in vitro flow model. Importantly, ACC_{max} decreased and the pressure gradient increased as the degree of the stenosis increased. ACC_{max}, ACC_{sys}, and peak systolic velocity were significantly different between the degrees of stenosis. Furthermore, ACC_{max} had the best coefficient of determination (R^2) to intraluminal pressure gradient (Table III). Therefore, it is possible to predict the degree of stenosis with ACC_{max}, and the use of a validated ACC_{max} measurement is a potentially suitable tool for diagnosing and assessing the severity of stenosis.

Results obtained using other noninvasive measurements for diagnosing PAD—including the ABI, TBI, and TP—can be either falsely elevated or falsely normal as a result of incompressible crural, pedal, and/or digital arteries[5,7,8]; this is particularly true for patients with a long history of diabetes, advanced age, and/or end-stage renal disease.[6] Van Tongeren et al[13] previously reported that ACC_{max} can serve as an accurate marker of PAD, regardless of the presence of diabetes (36 of 73 diabetic patients had ABI ≥ 1.30). A high ACC_{max} value (>10 m/s^2) can serve to exclude the presence of PAD, whereas an ACC_{max} value of <6.5 m/s^2 is strongly indicative of PAD. In addition, Buschmann et al[14] investigated ACC_{max} and showed a better ACC_{max} area under the curve for diagnosing PAD (defined as >50% diameter reduction on angiography) compared to ABI and relative pulse slope index in patients with and without diabetes. The sensitivity of ACC_{max} was superior to that of ABI in the overall sample. The specificity of ACC_{max} was similar to that of ABI in the overall sample and was superior in diabetic patients. Moreover, we measured ACC_{max} at a position distal to the stenosis, thereby avoiding any effects associated with medial calcific sclerosis. Thus, ACC_{max} has added value compared to currently available noninvasive diagnostic tests.

Young and Tsai[25] developed a formula for calculating pulsatile blood flow by combining pressure gradient, acceleration, and degree of stenosis, which reflect the effects of viscosity, turbulence, and inertia, respectively. As the degree of stenosis increases, the turbulence index becomes the dominant factor, as this value is calculated using the square of the degree of stenosis. As a result, the inertia index, which reflects acceleration (dU/dt), decreases as the degree of stenosis—and consequently the pressure gradient—increases. Thus, it can be concluded that acceleration tends to decrease as the degree of stenosis increases.[25] Furthermore, the length of a stenosis primarily affects energy loss. The effect of a change in length is less than the effect of a change in diameter. Because entrance and exit effects contribute a large portion of the resistance offered by a stenosis, doubling the length of a lesion has less impact than two separate lesions of equal length and diameter.[26] This correlates with our findings; with respect to both ACC_{max} and the pressure gradient, the setup with three 2-cm stenoses had the highest impact, and each 8-cm stenosis had a higher

impact compared to the corresponding 2-cm stenosis (Fig 5). However, the differences in ACC_{max} and pressure gradient were both not statistically significant between these groups.

Tehan et al[10] reported that both ABI and TBI have low accuracy with respect to diagnosing PAD in diabetic patients, with sensitivity values of only 45% and 64%, respectively. In another study, the same group investigated the accuracy of using TP to diagnose PAD and found that the receiver operating curve had an area under the curve of 0.76.[27] The authors found that the sensitivity and specificity of using TP to detect PAD in diabetic patients was approximately 74% and 72%, respectively; this was similar to their control nondiabetic group, which had a sensitivity and specificity of 67% and 71%, respectively. In addition, Sawka and Carter[9] previously reported that TP is dependent on temperature.

The reproducibility of ABI has been investigated in several studies, and the measurements varied by 9% to 21%.[28,29,30,31] De Graaff et al[31] found that the interobserver ICC for ABI was 0.92 and 0.87 when measured on the same day and 1 week later, respectively; similarly, the ICC for TP was 0.88 and 0.85, respectively. In addition, they found a 1-week interobserver repeatability coefficient of 27 and 41 mm Hg for ABI and TP, respectively. In our flow model study, we found an ICC value of 0.99 between two investigators who measured ACC_{max} at various degrees of stenosis. In addition, we found no significant difference in ACC_{max} when the distance from the stenosis was 30 or 20 cm, suggesting that ACC_{max} does not depend on the distance between the stenosis and the measurement point.

Previous research[13,15,16,17,18] and our study both show that ACC_{max} is a feasible noninvasive technique for assessing the severity of PAD and renal artery stenosis. In contrast, other duplex parameters are limited to identify the severity of a PAD (particularly at multilevel stenoses). Bardelli et al[15] investigated ACC_{max}, ACC_{sys}, and AT for diagnosing renal artery stenosis. This study showed better sensitivity, specificity, positive predictive value, and negative predictive value for ACC_{max} compared to ACC_{sys} and AT. Furthermore, the study described a potential source of bias in the measurement of ACC_{sys}, and AT is represented by the shape of the Doppler spectra. To circumvent this bias, maximal systolic acceleration (ACC_{max}) was introduced. Importantly, ACC_{max} has been shown to have diagnostic value in renal artery stenosis,[15,16,17,18] and van Tongeren et al[13] and Buschmann et al[14] showed that ACC_{max} is an accurate noninvasive tool for diagnosing PAD, also in diabetic patients who often have a higher degree of medial calcific sclerosis. In addition, determining the severity of PAD in patients with CLI can be challenging as a result of the presence of noncompressible arteries.[12] Sung et al[32] showed no consistent tendency of the influence of the compliance on the changes in peak systolic velocity, AT, or acceleration index, thus suggesting there is also no influence in ACC_{max} when the compliance changes, as in a calcified vessel. Therefore, we conclude that ACC_{max} can be clinically superior to other noninvasive measurements, particularly in patients with diabetes and/or CLI, as ACC_{max} is measured distal to the stenosis.

Additionally, ACC_{max} can be measured quickly (data acquisition time of less than 1 minute), in contrast to ABI and TP (more than 10 minutes).[14] Finally, duplex ultrasound is widely available and relatively inexpensive, the measurements can be easily obtained from the ankle or digital arteries, and the technique is suitable for patients who cannot undergo angiography.

This study has several limitations and possible caveats that warrant discussion. ACC_{max} measured in an in vitro circulatory system may not fully reflect ACC_{max} measured in vivo in a human artery; additionally, this flow model was primarily validated for aortic circulation. However, although the flow curve was biphasic in our in vitro circulatory system, both intraluminal MAP and ACC_{max} measured without a stenosis were the same as in a patient. The collateral circulation in this in vitro circulatory system went directly to the reservoir. Hence, no impact of collateral circulation was measurable in our model. This study focused on the trend of the ultrasound parameters measured at various degrees of stenosis and on the association between ACC_{max} and the intraluminal pressure gradient but did not examine possible cutoff values, which was beyond the scope of the study. Given the clinical relevance of examining a cutoff value for diagnostic criteria for PAD, this will be investigated in a subsequent study. Because it was not possible to measure ABI or TP in our in vitro flow model, we chose to use the intraluminal pressure gradient as a measure of the severity of the stenosis. Buschmann et al[14] recently introduced a computer algorithm for ACC_{max}; in our study, we used a computer-based calculated ACC_{max} at a single representative curve. The high interobserver ICC in our study may not necessarily reflect the interobserver ICC when measuring in a human artery in vivo. The high ICC in our study could have been because we used relatively large intervals in terms of the degree of stenosis (ie, no stenosis, 50%, 70%, 80%, and 90%). Thus, the ICC for ACC_{max} measured in patients should be examined in a clinical setting.

Conclusions

We report a close correlation between ACC_{max} and the MAP gradient measured using an in vitro flow model. Specifically, we found that ACC_{max} decreased as the severity of stenosis increased. Furthermore, because of the low interobserver variability and the wide availability of the required equipment, measuring ACC_{max} may provide a robust new noninvasive technique for assessing the severity of PAD. ACC_{max} should be evaluated thoroughly in a clinical study involving patients in order to test its clinical value.

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Chapter 4

Doppler ultrasonography Derived maximal systolic acceleration: value determination with artificially induced stenosis

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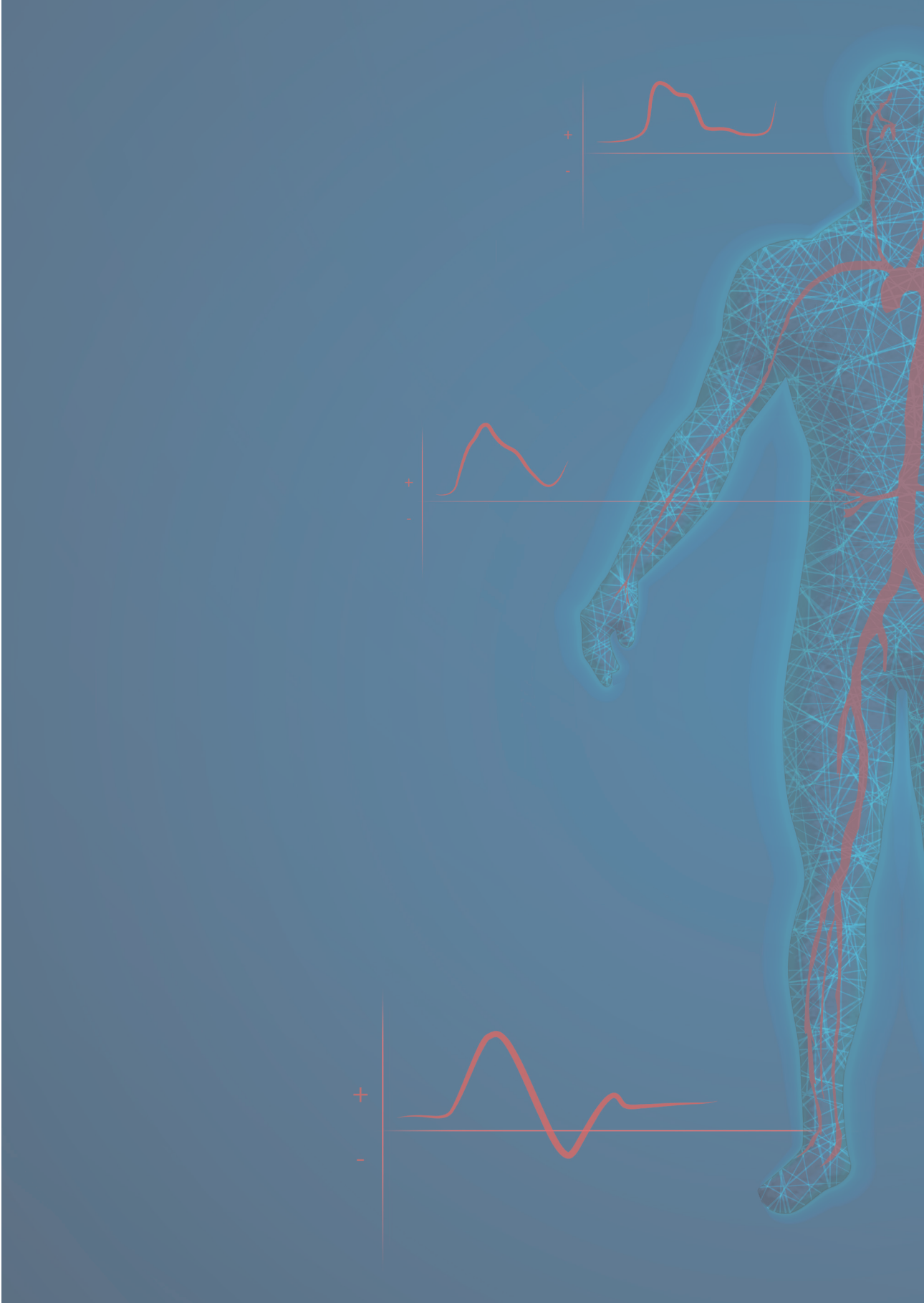

Abstract

Background

In diagnosing peripheral arterial disease (PAD), medial arterial calcification (MAC) hampers arterial compression and could lead to unreliable ankle brachial index (ABI), toe brachial index (TBI) and toe pressure (TP). Doppler ultrasonography (DUS) derived maximal systolic acceleration (ACCmax) might be more accurate to diagnose PAD. In an in vitro study, a strong correlation between ACCmax and the severity of stenotic disease was determined. The aim of this study was to investigate the ACCmax in correlation with conventional non-invasive diagnostics in an in vivo setting.

Methods

In twelve healthy individuals, an arterial stenosis was mimicked by compression on the common femoral artery by an ultrasounds probe, creating a local stenosis of 50%, 70% and 90%. The ABI, TBI, TP and several DUS parameters (including ACCmax) were assessed at the ankle during these different degrees of stenosis. All DUS parameters were measured separately by two observers to determine the interobserver variability.

Results

Overall the ABI, TBI, TP, ACCmax, ACCsys and PSV decreased significantly when the degree of stenosis increased. The ACCmax showed the highest correlation with the degree of stenosis (r −.884), compared to ABI (r −.726), TBI (r −.716) and TP (r −.758). Furthermore, the interobserver variability of ACCmax was excellent, with an intraclass correlation coefficient (ICC) of .97.

Conclusion

ACCmax is an accurate non-invasive DUS parameter to diagnose and assess the severity of a mimicked arterial stenosis in healthy individuals. Further prospective assessment of the clinical value of ACCmax and its potential benefits in patients with PAD is needed.

Introduction

The severity of peripheral arterial disease (PAD) is primarily assessed by the ankle brachial index (ABI), toe brachial index (TBI) and toe pressure (TP).[1] However, due to incompressible arteries in patients with medial arterial calcification (MAC), the ABI, TBI and TP can be falsely elevated leading to unreliable results.[2-5] MAC is mostly seen in patients with diabetes mellitus (DM), chronic kidney failure and elderly patients.[6] In these patients, ABI, TBI and TP will therefore not provide an adequate estimation of the blood flow to foot and toes.[7,8] The prevalence of PAD in people with DM is 20–30%,[9] and increases to 65% in patients with diabetic foot ulcer (DFU).[10] MAC can be present in up to a third of patients with DM,[11] and in patients with critical limb ischemia (CLI) circa 20% have incompressible arteries.[12] For these patients, an alternative non-invasive accurate diagnostic parameter is needed to assess the severity of PAD.

Two recent reviews showed the poor results and insufficient evidence of bedside tests for diagnosing PAD among patients with DM. These authors advocated for more studies and an alternative diagnostic technique.[7,8] A relatively new Doppler ultrasonography (DUS) parameter, maximal systolic acceleration (ACCmax), can be used in detecting PAD and better estimating its severity independently of blood pressure measurements.[5,13,14] It measures the acceleration of blood flow by quantifying the maximal slope of the systolic doppler curve. Recently, our in vitro study showed that the ACCmax decreased as the severity of stenosis increased. Also, a strong correlation was found between the ACCmax and the intra-arterial pressure gradient.[13] ACCmax has potentially important benefits compared to the conventional non-invasive bedside tests regarding the influence of incompressible arteries.[5,8,13-15]

To further investigate the value of ACCmax in PAD, an in vivo study was conducted with artificially created arterial stenosis in healthy individuals. The aim of this study was to compare the ACCmax with conventional non-invasive arterial pressure measurements and other DUS parameters to determine the severity of arterial stenosis

Materials and Methods

Ethical Considerations

This study follows the declaration of Helsinki. The medical ethical committee of the tertiary academic hospital granted permission to perform this study (P16.251). Participation was voluntarily and without obligation. All the study participants received a clear letter of information and signed informed consent.

Design

In this prospective in vivo study, the study population consists of healthy male participants between 18 and 30 years old with a normal circulation. Subjects were not included when suffering from PAD, DM, cardiac disease, or other vascular diseases (among other things Raynaud's phenomenon or vasculitis).

In this study, a developed test setup was used, as shown in figure 1. The instrumental affairs department of the academic hospital made a robust adjusting arm, which was attached to the examination bed (figure 1(a)). On the other side of the arm, an ultrasound transducer was attached to the white holder (figure 1(b)), a Z-One Zonare duplex device with a transducer L 10-5 was used. Due to the adjustable screw construction (figure 1(b)), the ultrasound transducer was able to acquire well-balanced compression on the common femoral artery (CFA), creating a modifiable stenosis in the CFA. Because an ultrasound transducer was used to get compression on the CFA, the degree of stenosis was directly obtained by duplex as reference test. The degree of compression can be adjusted using the screw construction, adjusting the height and thereby the extent of compression of the ultrasound transducer. Hence, the transducer that was connected to the arm was bifunctional: causing and also directly showing the degree of stenosis. Figure 1(c) shows an overview of the test setup. In our test setup, 2 DUS devices were used: one causing and measuring the degree of stenosis in the CFA, the other device measuring the DUS parameters (including the ACCmax) at the posterior tibial artery. Three degrees of stenosis were obtained: 50%, 70% and 90% by compression on the CFA. During these measurements, there was a continuous monitoring of the obtained degree of stenosis in the CFA. After about 30 seconds, to confirm the stenosis was stable, the following measurements were obtained at the posterior tibial

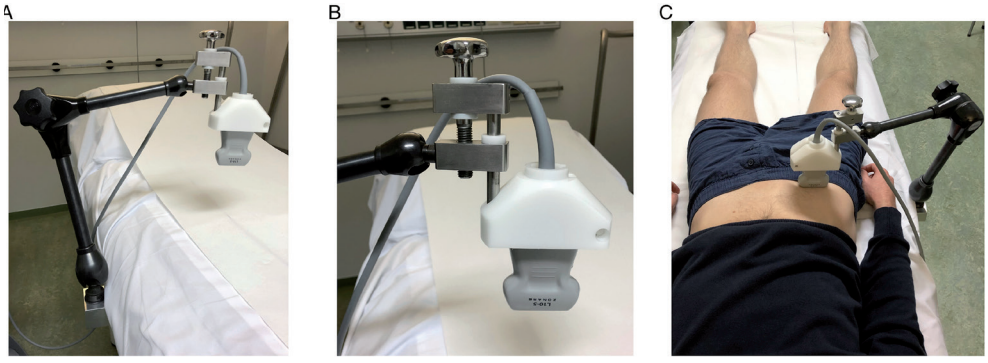

Figure 1. Overview of the test setup. A: the adjusting arm is displayed. B: the ultrasound transducer was attached to the white holder of the adjusting arm. By the screw construction it was possible to obtain compression on the CFA. C: An overview of the experimental test setup is displayed.

artery: the ABI, TBI, TP, ACCmax, mean systolic acceleration (ACCsys), acceleration time (AT) and peak systolic velocity (PSV). Due to the method of local compression on the CFA, the artery disformed into an oval shape instead of a concentric stenosis, therefore reduction in cross-sectional area was used to determine the degree of stenosis, instead of the diameter reduction measurement.

In case of emergency, the modified arm could be simply removed by a separate screw construction, this procedure was not necessary during the study.

Doppler Ultrasonography

All DUS measurements were done by two separate investigators, using an Acuson S2000 System, Helix Evolution (Siemens Medical Solutions, Ultrasound Division, Issaquah) equipped with a 9L4 9-4 MHz linear transducer. All measurements were performed with a fixed 60-degree angle of insonation. To determine the interobserver variability, the two investigators were unaware of the measurements of each other. However, the investigators were aware of the degree of stenosis. The ACCmax was calculated by a computer at a single representative curve, as described in Brouwers et al.[13] The ACCmax occurs at the maximal slope in the systolic phase and is expressed in m/sec.^{2} Figure 2 shows an example of a normal and a divergent waveform including ACCmax measurements. No additional software is necessary to obtain the ACCmax. 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. The computer automatically calculates the acceleration of the tangent line in m/sec^2 (= maximal systolic acceleration). The ACCmax is always measured distal to the stenosis (for example, at the distal posterior tibial artery). In an in vitro study, it is

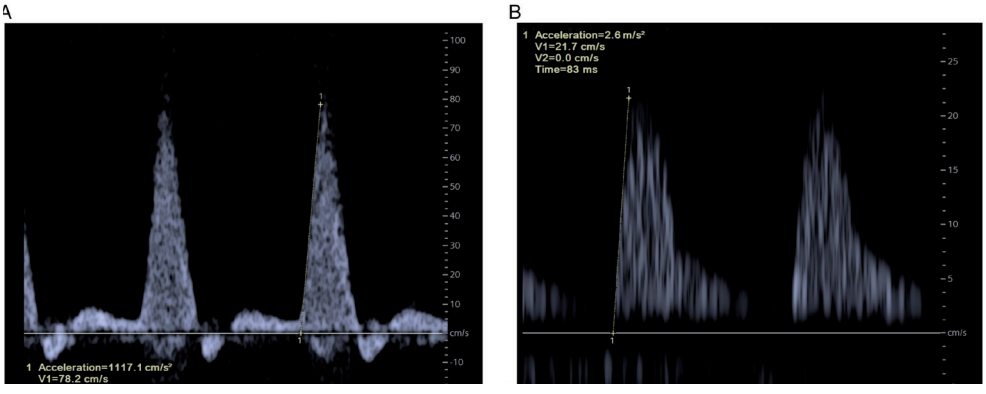

Figure 2. Doppler waveforms. A: a normal waveform is shown without the presence of peripheral arterial disease (ACCmax 11.2 m/sec^2). B: a post stenotic signal in the tibialis posterior artery is obtained with a decreased ACCmax (2.6 m/sec^2). In both figures, the ACCmax is measured at the maximal slope in the systolic phase. Note the differences in scales between the figures.

suggesting that the ACCmax does not depend on the distance between the stenosis and the measurement point.[13] ACCmax should not be confused with either acceleration time (AT) or mean systolic acceleration (ACCsys). ACCsys is the slope between the beginning of the systolic upstroke and the peak of systole and is calculated using the following equation: $ACC_{sys} = \Delta V_{sys}/AT$.

Statistical Analysis

The power analysis of this study was based on a paper of Julious et al,[16] which describes that for an explorative study looking at means and standard deviations, 12 test subjects are required. All statistical analyses were performed using SPSS statistics 25.0 software ® (IBM, Armonk, NY). Mixed model analysis was used to determine if there are overall differences between a parameter at multiple test setups (degree of stenosis). A Bonferroni correction was applied for each parameter to correct for multiple testing of different test setups (no stenosis vs 50% stenosis, 50% stenosis vs 70% stenosis, and 70% stenosis vs 90% stenosis). Differences with $P < .05$ were considered statistically significant. Following a bivariate correlation analysis, the correlation between parameters was calculated by Pearson's r. A Pearson's r of >70 is considered a high correlation, .50–.70 refers to a moderate correlation. The interobserver variability was assessed using an intraclass correlation coefficient (ICC). An ICC of >.90 indicates an excellent agreement between the different observers.

Results

Twelve healthy subjects participated in the present study, without any dropouts. The following target test setups were applied to the test subjects: no stenosis, 50%, 70% and 90% degree of stenosis. Looking at the degree of stenosis, as shown in Table 1, a corresponding stenosis degree was created using compression by the inguinal ultrasound transducer on the CFA. These actual test setups were: no stenosis, 50% (±1.8), 70% (±1.1) and 89% (±1.2), which were reliable values for this investigation. All tests were well tolerated by the subjects; there were no obvious pain complaints. Subjects did experience temporary discomfort by pressure in the groin, and a pins and needles sensation in the leg at high grade stenosis.

Table 2 shows an overview of the assessed parameters at different test setups. Upon increasing degrees of CFA stenosis, overall a significant reduction was seen in ABI ($P < .001$), TBI ($P < .001$), TP ($P < .001$), ACCmax ($P < .001$), ACCsys ($P < .001$) and PSV ($P<.001$). Furthermore, AT was significantly increasing ($P < .001$) when increasing the degree of stenosis.

Target test setups	Mean actual degree of stenosis
no stenosis	No stenosis
50%	50% (±1.8)
70%	70% (±1.1)
90%	89% (±1.2)

Table 1: Overview of different test setups.
The standard deviation (±SD) is given in percent. The degree of stenosis is given in reduction in cross-sectional area.

	No stenosis	50% stenosis	70% stenosis	90% stenosis
ABI	1.1 (±0.11)	0.99 (±0.14)	0.89 (±0.15)	0.59 (±0.22)
TBI	0.93 (±0.15)	0.86 (±0.16)	0.75 (±0.14)	0.51 (±0.16)
TP	122 (±18)	113 (±21)	98 (±14)	65 (±16)
ACCmax	8.6 (±0.9)	7.5 (±2.5)	4.6 (±1.0)	1.0 (±0.5)
ACCsys	6.5 (±1.1)	5.6 (±1.7)	3.9 (±1.1)	0.9 (±0.3)
AT	85 (±13)	80 (±16)	91 (±17)	116 (±27)
PSV	52 (±12)	45 (±16)	33 (±8.3)	15 (±13)

Table 2: Overview of assessed parameters.
The mean ankle brachial index (ABI), toe brachial index (TBI), toe pressure (TP) in mm Hg, maximal systolic acceleration (ACCmax) in m/sec^2, mean systolic acceleration (ACCsys) in m/sec^2, acceleration time (AT) in in milliseconds and peak systolic velocity (PSV) in cm/sec are given for the different test setups, including the standard deviation (SD). The degree of stenosis is given in cross-sectional area reduction.

Figure 3 depicts boxplots for all parameters, the Bonferroni adjusted P-values were determined between every test setup (no stenosis vs 50% stenosis, 50% stenosis vs 70% stenosis, and 70% stenosis vs 90% stenosis): for ABI P = .308, P = .330, P < .001*; for TBI P = .615, P = .094, P < .001*; TP P = .763, P = .100, P < .001*; for ACCmax P = .287, P < .001*, P < .001*; for ACCsys P = .177, P = .001*, P < .001*; for AT P = 1.000 P = .422, P = .001*; and for PSV P = .203, P = .003*, P < .001*, respectively.

The correlation coefficient between parameters and also with the degree of stenosis is shown in Table 3. In our analysis, the ACCmax had the best correlation (r –.884) to the degree of stenosis, followed by ACCsys (r –.861), TP (r –.758), PSV (r –.741), ABI (r –.726), TBI (r –.716) and AT (r .503). The ACCmax was also highly correlated to ACCsys (r .969), ABI (r .782) and TP (r .743).

Correlation analysis		Pearson correlation coefficient r (all with P-value <0.01)
ACCmax	Stenosis degree	**-0.884**
	ABI	0.782
	TBI	0.697
	TP	0.743
	ACCsys	0.969
	AT	-0.602
	PSV	0.797
ABI	Stenosis degree	**-0.726**
	TBI	0.850
	TP	0.809
	PSV	0.554
	ACCsys	0.782
	AT	-0.684
TBI	Stenosis degree	**-0.716**
	TP	0.954
	PSV	0.628
	ACCsys	0.709
	AT	-0.464
TP	Stenosis degree	**-0.758**
	PSV	0.719
	ACCsys	0.762
	AT	-0.448
ACCsys	Stenosis degree	**-0.861**
	PSV	0.804
	AT	-0.606
AT	Stenosis degree	**0.503**
	PSV	-0.304
PSV	Stenosis degree	**-0.741**

Table 3: Overview of the correlation coefficients between the degree of stenosis and parameters. Ankle brachial index (ABI), toe brachial index (TBI), toe pressure (TP), maximal systolic acceleration (ACCmax), mean systolic acceleration (ACCsys), acceleration time (AT), and peak systolic velocity (PSV).

Interobserver Variability

All DUS parameters were measured by two independent investigators to obtain the interobserver variability in this in vivo study. As shown in Table 4, the intra class correlation coefficient (ICC) was .97 for ACCmax. Also, PSV had an excellent agreement in the measurements with an ICC of .91. ACCsys and AT had a good level of agreement, respectively, an ICC of .71 and .72.

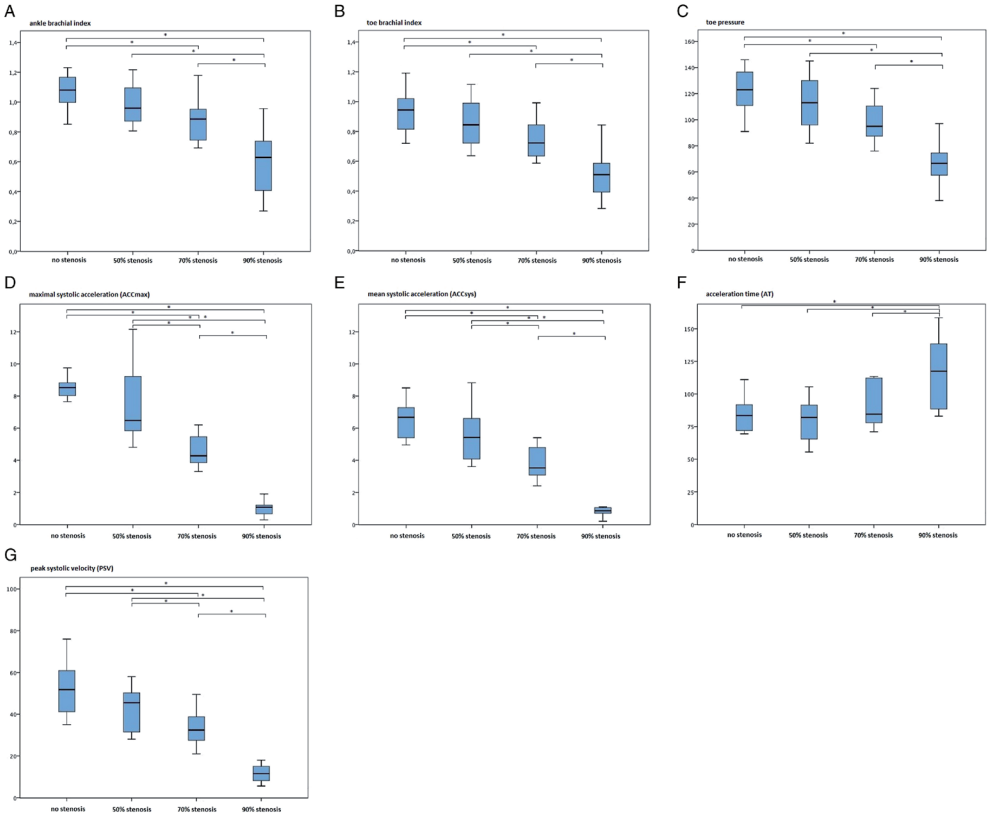

Figure 3. Boxplots of diagnostic parameters for different test setups. A: ankle brachial index (ABI), B: toe brachial index (TBI), C: toe pressure (TP) in mm Hg, D: maximal systolic acceleration (ACCmax) in m/sec^2, E: mean systolic acceleration (ACCsys) in m/sec^2, F: acceleration time (AT) in milliseconds and G: peak systolic velocity (PSV) in cm/sec. The boxplots are representing the median, 25% quantile, 75% quantile and 1.5 interquartile range (top and bottom whiskers) per test setup. Statistically significant differences ($P < .05$) between test setups are marked with *.

	Intra class correlation coefficient (ICC)
ACCmax	0.97
ACCsys	0.71
AT	0.72
PSV	0.91

Table 4: The interobserver variability for different DUS parameters.
Maximal systolic acceleration (ACCmax), mean systolic acceleration (ACCsys), acceleration time (AT), and peak systolic velocity (PSV).

Discussion

In the present study, PAD was mimicked in an in vivo setting by controlled local compression on the common femoral artery in healthy study participants. A strong correlation was found between ACCmax and the degree of an artificially introduced stenosis. The ACCmax proved to be superior to ABI, TBI, TP, ACCsys and PSV and had an excellent interobserver variability. Therefore, ACCmax measurement is a promising reliable non-invasive tool to assess the severity of PAD.

Previous studies indicated that the ACCmax can be used as an accurate PAD diagnostic marker, even in patients with DM.[5,13,14] Similar to our in vitro study,[13] in this in vivo study a strong correlation between the ACCmax and the degree of stenosis was demonstrated (r −.884). In addition, our previous in vitro study showed a good correlation between the ACCmax and the intra-arterial pressure gradient (R^2 .937). A high ACCmax value precludes a hemodynamic inflow problem and excludes the presence of PAD proximal of its measuring point. In the present study, in a hemodynamically significant stenosis of 70% reduction in cross-sectional area, a mean ACCmax of 4.6 m/sec^2 was found. This is in accordance with the previous results of our group indicating that a high ACCmax (>10 m/s^2) can exclude the presence of PAD with a negative predictive value of 95%. An ACCmax of below 6.5 m/s^2 is strongly indicative of PAD with a positive predictive value of 99%. In that paper, it is concluded that the ACCmax is an accurate marker that could offer significant benefits for the diagnosis of PAD, especially in DM.[5] Buschmann et al revealed a threshold of 5.0 m/s^2 for diagnosing PAD (based on digital subtraction angiography), and showed a better ACCmax area under the curve compared to ABI and relative pulse slope index in patients with and without DM.[14] So, ACCmax appears to be more accurate in detecting PAD than the conventional non-invasive pressure measurements. Additionally, there are some practical advantages of using ACCmax. It can be measured at any point in the artery, hence avoiding effects associated to a local calcified plaque. Furthermore, ACCmax measurements can be obtained in a very short time (data acquisition time of less than 1 minute), in contrast to ABI, TBI and TP (more than 10 minutes).[14]

There are several considerations to be made in favour of ACCmax measurements. ABI, TBI and TP are prone to be falsely normal or elevated due to incompressible peripheral arteries, especially in elderly patients that have a history of DM or have suffered from renal disease for a longer period of time, resulting in medial arterial calcification (MAC).[6,14,17-19] ABI and TBI have a rather low sensitivity for diagnosing PAD in patients with DM, with a sensitivity of 45% and 64%, respectively.[20] In addition, slightly higher numbers have been reported on the sensitivity and specificity of TP for diagnosing PAD in patients with DM, respectively, 74% and 72%.[21] In contrast to external blood pressure measurements (ABI, TBI and TP), DUS measurements circumvent this limitation regarding MAC.[8] By measuring ACCmax, there is

no external blood pressure measurement that can be influenced by vessel stiffness. Sung et al showed no influence of vessel compliance (as in vessels with MAC) on the changes in peak systolic velocity (PSV), acceleration time (AT), or acceleration index (AI),[15] suggesting ACCmax is also not affected by vessel compliance changes. In clinical studies, there has been concluded ACCmax can be used to diagnose PAD accurately in patient with high risk of MAC.[5,14] Therefore, the ACCmax is also a potential accurate measurement of perfusion in patients with DM, independently of presence of MAC.

With respect to the reproducibility, a wide range of results was published for ABI.[22-25] De Graaff et al showed an interobserver variability (ICC) for ABI of .92 and for TP of .88 at the same day. Moreover, a 1-week interobserver repeatability coefficient of 27% and 41 mm Hg for ABI and TP were found, respectively.[25] In accordance with the results of the previous in vitro study,[13] an excellent agreement for ACCmax was revealed in the present study, ICC .99 and .97, respectively. Since these studies were experimental (in vitro and in vivo) care must be taken when comparing it to the results of de Graaff et al.

The highest clinical value of the ACCmax lies in a hemodynamically significant stenosis (≥ 70% reduction in cross-sectional area). In the present study, there is a relative wide spread in ACCmax at a hemodynamically non-significant stenosis of 50% in cross-sectional area (figure 3(d)), resulting in a non-significant difference between the ACCmax at no stenosis and 50% stenosis. This might be explained by the fact that an acute stenosis was made in young and healthy test subjects. A visual observation of the investigators was that the cardiac output increased (increased stroke volume on DUS-images, however this was not objectified by measurements) as a reaction on the 'first acute' stenosis. Therefore, the ACCmax could be increased at some young healthy test subject at a 50% stenosis compared to a non-stenosis. This will probably not occur in patients with PAD since this disease has a more chronic character. Still the ACCmax decreases at a hemodynamically significant stenosis, even in young healthy test subjects. Moreover, in the previous in vitro study, there was a normal decrease in ACCmax between no stenosis and 50% stenosis (diameter reduction) since the 'cardiac output' was unchanged during the different test setups.[13] Despite the relative wide spread at a 50% stenosis in this study, the ACCmax had a higher correlation with the degree of stenosis compared to ABI, TBI, TP and other DUS parameters.

Limitations

Apart from complex clinical settings that occur in reality (eg impact from cardiac output, shear rate, collateral circulation, vascular compliance and outflow obstruction), this in vivo study investigated basic principles: the impact of different artificial stenosis in healthy subject and compared the ACCmax with conventional non-invasive pressure measurements and DUS parameters. Since the study population consisted of healthy participants, only an

artificial single stenosis could be mimicked, while the real PAD patient has often multi-level disease. However, the previous in vitro study revealed a comparable trend with respect to both ACCmax and intra-arterial pressure gradient at multi-level disease.[13] Furthermore, in the present study, compression of the artery was provided by an ultrasound probe, resulting in an oval shape and smooth surface of the artery, which might distort the results compared to a more rough and irregular arterial stenosis. Note that the degree of stenosis is given in reduction in cross-sectional area as a result of the oval shape of the artificial stenosis. The high ICC in this study might be due to the relatively large intervals in terms of the degree of stenosis (no stenosis, 50%, 70% and 90%). Hence, the high ICC for ACCmax must be interpreted with caution and should be examined in patients in a prospective clinical setting.

Conclusion

The present study contributes to further evaluation of ACCmax to diagnose and assess the severity of peripheral arterial disease (PAD). The ACCmax correlates more accurately with the degree of stenosis than conventional non-invasive pressure measurements and other DUS parameters in artificially introduced arterial stenosis in healthy individuals. ACCmax measurement can be obtained with a low interobserver variability. Along with the potential benefits of ACCmax concerning MAC, it may provide a reliable new non-invasive technique in PAD. Future investigation in ACCmax is needed in patients with PAD to obtain its exact clinical value and the potential benefits in PAD.

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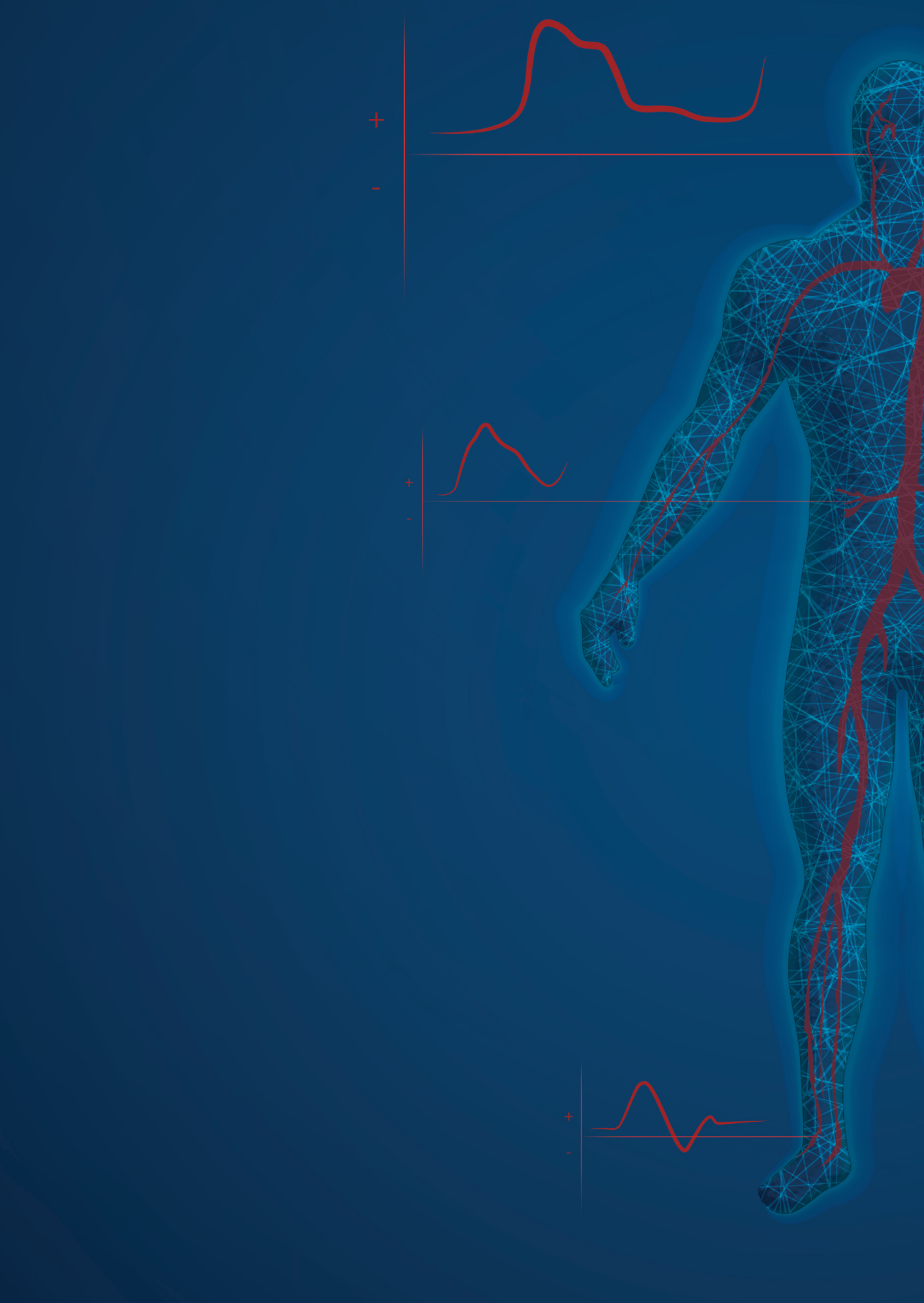
Part II

Carotid artery stenosis



Chapter 5

A new Doppler-derived parameter to quantify internal carotid artery stenosis: maximal systolic acceleration

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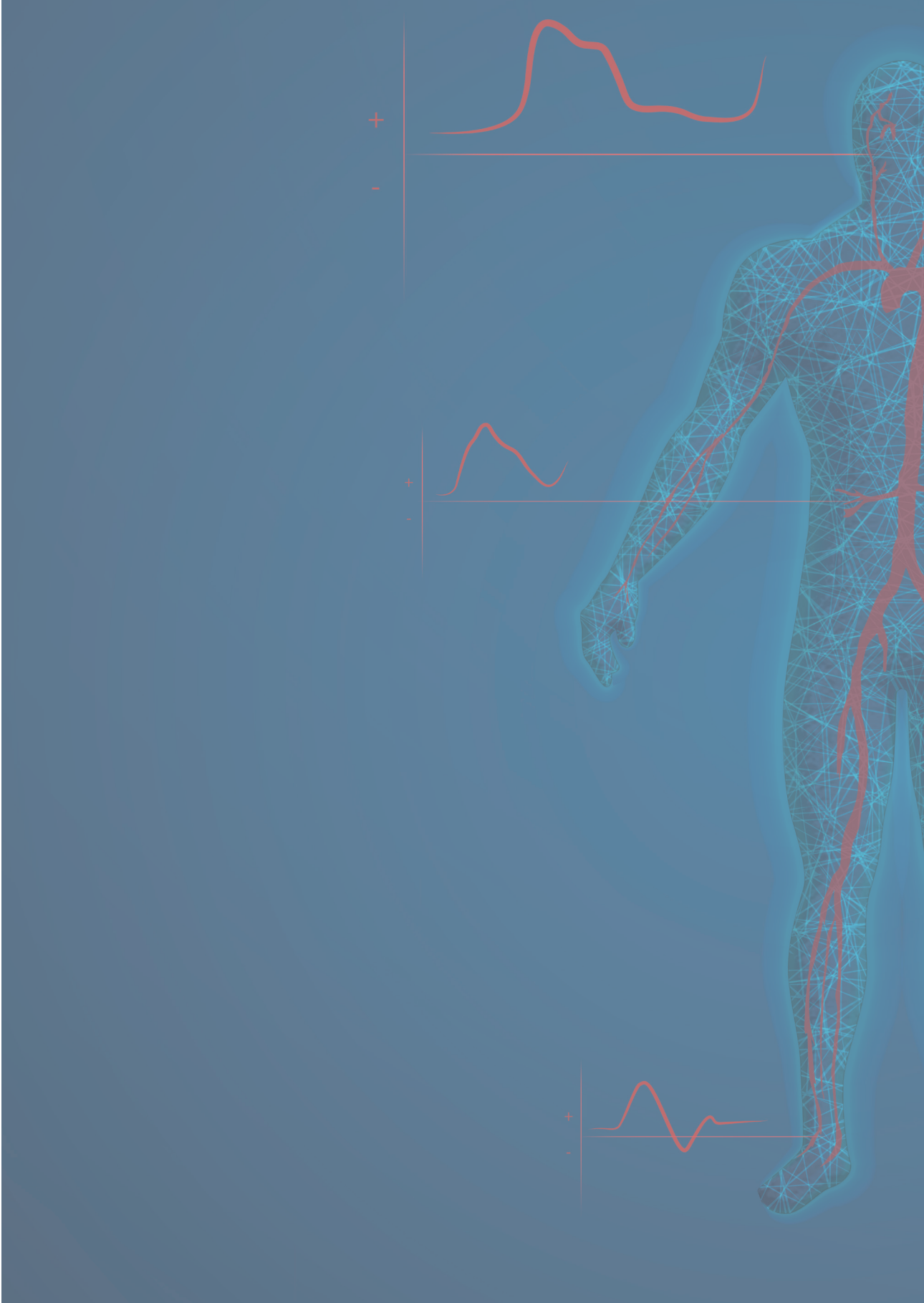

Abstract

Background

Doppler ultrasonography (DUS) is used as initial measurement to diagnose and classify carotid artery stenosis. Local distorting factors such as vascular calcification can influence the ability to obtain DUS measurements. The DUS derived maximal systolic acceleration (ACCmax) provides a different way to determine the degree of stenosis. While conventional DUS parameters are measured at the stenosis itself, ACCmax is measured distal to the internal carotid artery (ICA) stenosis. The value of ACCmax in ICA stenosis was investigated in this study.

Methods

All carotid artery DUS studies of a tertiary academic center were reviewed from October 2007 until December 2017. Every ICA was included once. The ACCmax was compared to conventional DUS parameters: ICA peak systolic velocity (PSV), and PSV ratio (ICA PSV/ CCA PSV). ROC-curve analysis was used to evaluate accuracy of ACCmax, ICA PSV and PSV ratio as compared to CT-angiography (CTA) derived stenosis measurement as reference test.

Results

The study population consisted of 947 carotid arteries and was divided into 3 groups: <50% (710/947), 50–69% (109/947), and ≥70% (128/947). Between these groups ACCmax was significantly different. Strong correlations between ACCmax and ICA PSV (R^2 0.88) and PSV ratio (R^2 0.87) were found. In ROC subanalysis, the ACCmax had a sensitivity of 90% and a specificity of 89% to diagnose a ≥70% ICA stenosis, and a sensitivity of 82% and a specificity of 88% to diagnose a ≥50% ICA stenosis. For diagnosing a ≥50% ICA stenosis the area under the curve (AUC) of ACCmax (0.88) was significantly lower than the AUC of PSV ratio (0.94) and ICA PSV (0.94). To diagnose a ≥70% ICA stenosis there were no significant differences in AUC between ACCmax (0.89), PSV ratio (0.93) and ICA PSV (0.94).

Conclusions

ACCmax is an interesting additional DUS measurement in determining the degree of ICA stenosis. ACCmax is measured distal to the stenosis and is not hampered by local distorting factors at the site of the stenosis. ACCmax can accurately diagnose an ICA stenosis, but was somewhat inferior compared to ICA PSV and PSV ratio to diagnose a ≥50% ICA stenosis.

Introduction

Carotid artery stenosis has long been recognized as an important etiological factor for ischemic stroke and large trials have determined the benefit of carotid endarterectomy (CEA) in symptomatic patients as prophylactic countermeasure against stroke.[1.,2.,3.,4.,5.] Doppler ultrasonography (DUS) is the primary evaluation of carotid artery stenosis and management determination.[6.,7.,8.] Although in many centers additional imaging (computed tomographic angiography (CTA) or MR angiography (MRA)) is obtained when intervention is considered, in some regions a majority of surgical interventions of the carotid artery is based on DUS-imaging alone.[9.] Furthermore, the European and American guidelines mention the option of DUS alone to make a decision regarding intervention.[6.,7.] Therefore, the accuracy of this imaging technique is of the utmost importance.

According to the Society of Radiologists in Ultrasound Consensus Conference the evaluation of carotid artery stenosis with DUS-imaging relies on four parameters: peak systolic velocity (PSV) in the internal carotid artery (ICA), optical estimation of the stenosis, PSV ratio (PSV ICA/PSV common carotid artery (CCA)), and the end diastolic velocity (EDV) in the ICA.[8.] While these parameters together provide an informative basis to determine and grade a stenosis, all four parameters are measured at the level of the stenosis and can therefore be influenced by local distorting factors. Presence of calcified atherosclerotic plaques and near occlusions can hamper these measurements and potentially lead to inaccurate estimation of degree of ICA stenosis.[8.,10.,11.,12.,13.]

A relatively new velocimetric doppler-derived parameter, maximal systolic acceleration (ACCmax), has been evaluated in atherosclerotic diseases.[14.,15.,16.,17.,18.,19.,20.] Recently we established in an in vitro study that a decreased ACCmax correlated very well with an increasing severity of stenosis, and a good correlation was found between the ACCmax and the intra-arterial pressure gradient (coefficient of determination (R^2) of 0.937).[14.] A high ACCmax value endorses that there is no hemodynamic inflow problem and excludes the presence of peripheral artery disease.[16.] At the moment, ACCmax has not been evaluated in carotid artery atherosclerotic disease. A potentially benefit of ACCmax to evaluate the degree of carotid artery stenosis is the ability to perform the measurement distal from the stenosis, herewith avoiding the influence of local distorting factors, such as acoustic shadowing as a result of vascular calcification. Therefore, ACCmax could be an interesting additional feature in determining the degree of carotid artery stenosis. In this retrospective study we focused on the diagnostic value of ACCmax in a large group of ICA stenosis, as compared to conventional DUS parameters. To investigate which parameter is the most accurate one, various DUS parameters were compared to CTA as reference test.

Methods

The institutional Medical Ethical Board approved this retrospective study. Patient data were reviewed using a local database of a tertiary academic center to identify all individuals who underwent carotid artery DUS-imaging, during the period from October 2007 until December 2017.

Measurements were excluded when DUS-imaging was performed for another reason than determining atherosclerotic ICA stenosis, including carotid body tumor, aneurysm or dissection. ICA's showing an occlusion were excluded. Carotid vessels with a stent and after CEA were excluded, since both these interventions may change the ipsilateral velocimetric properties of blood flow.[21.,22.,23.] Carotid arteries showing near occlusion were excluded since ipsilateral velocities may be high, low, or undetectable.[8.] An occlusion or >70% stenosis of the ICA is known to increase velocimetric values in the carotid artery on the contralateral side; so, their contralateral ICAs were also excluded.[24.,25.] After intervention the contralateral ICA was not excluded. Some patients had more than one DUS measurement during the study period. The repeated DUS measurements were excluded, so every ICA was included only once. Furthermore, patients with a proximal stenosis of the supra-aortic arteries (brachiocephalic and common carotid artery) were excluded. Lastly, DUS-imaging reports missing one or more critical velocimetric parameter values (CCA PSV, ICA PSV, and ACCmax in the distal ICA), were excluded.

Doppler Ultrasonography

All Doppler ultrasound procedures were performed by the same vascular ultrasound specialist, using an Acuson S2000 System (Siemens Medical Solutions, Ultrasound Division, Issaquah, Wash) equipped with a 9L4 9-4 MHz linear and convex transducer. PSV ratio was measured by the PSV in the ICA at the level of the stenosis divided by PSV in the CCA. The study population was divided into the following categories: <50% stenosis, 50–69% stenosis, and ≥70% stenosis (occlusions and near occlusions were excluded), as determined on several parameters as described by Grant et al.[8.] The ACCmax was calculated by computer at a single representative curve, as described in Brouwers et al. and is expressed in m/sec^2.[14.] The ACCmax occurs at the maximal slope in the systolic phase (see figure 1) and is measured distal to the stenosis. For an ICA stenosis the ACCmax is measured as distal as possible (extracranial), at least 2 cm distal of the ICA bulb. 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/sec^2 (= maximal systolic acceleration). ACCmax should not be confused with either acceleration time (AT) or mean

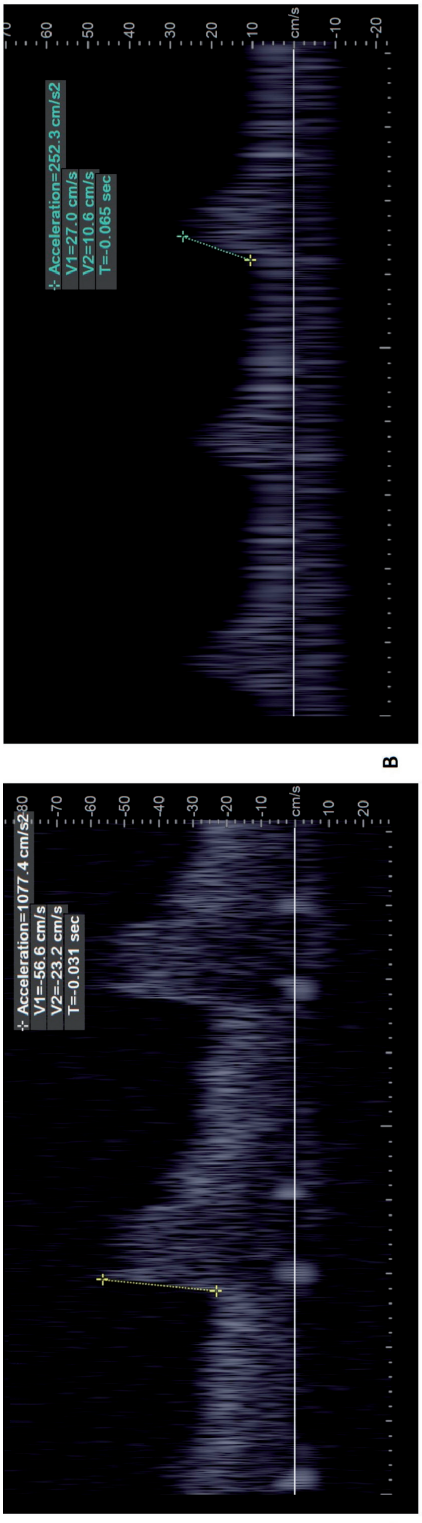

Fig. 1: Doppler waveforms from the distal extracranial ICA. (A) a normal waveform is shown without a stenosis (ACCmax 10.8 m/s2); (B) a post stenotic signal at 70–99% ICA stenosis is obtained with a decreased ACCmax (2.5 m/s2). In both figures, the ACCmax is measured at the maximal slope in the systolic phase.

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.

Computed Tomography Angiography (CTA)

DUS parameters (ACCmax, ICA PSV or PSV ratio) were compared to ICA stenosis measurement on CTA as reference test in a subgroup of patient, to investigated which DUS parameter is the most accurate for detecting carotid artery stenosis. CTAs which were performed in a period of six months before or after DUS examination of the study population, were included in the present study. CTA of carotid arteries was performed in patients with a ≥50% stenosis on DUS or debatable cases, therefore the number of CTA-imaging was less compared to DUS-studies. All included CTAs were re-examined by one radiologist (4 years of experience) blinded to the DUS results and the radiological reports of the initial examination, in order to determine the degree of stenosis. CTAs with poor image quality due to movement or insufficient contrast were excluded. All CTA examinations were performed using a 64-row or 320-row multidetector CT (Acquilion 64 and Acquilion-One Canon Medical Systems, Otawara, Japan). CTA acquisition was performed after intravenous injection of 70-75 ml of nonionic contrast medium (Ultravist 370; Bayer HealthCare) at 4.0–4.5 mL/s followed by a saline bolus of 40 mL at the same flow rate. A standard protocol was used, with 120kVp and 350 mA. Diameter reduction NASCET-style ratios were calculated for each carotid artery stenosis.[1,] Semi-automated measurements were performed on a dedicated workstation (Vitrea, version 6.8; Vital Images). The vessel of interest was manually selected and subsequently the software automatically determined the center lumen line. After visual inspection the radiologist selected the segment of the ICA with the narrowest diameter and a distal normal post-stenotic segment as the reference site. The parameters that were then automatically assessed where the minimal and maximal vessel lumen diameters of the selected segment. All the results were verified at the perpendicular views and manually corrected if the minimal or maximal diameter was under- or overestimated. Marquering et al. showed an excellent reproducibility for this semi-automated method.[26,]

Statistical Analysis

The correlation between conventional velocimetric values (ICA PSV and PSV ratio) and the ACCmax was analyzed using the Pearson linear correlation test. The relation between ACCmax and conventional duplex parameters was fitted with nonlinear regression using the model: ACCmax ~ $a/x + b/x^2$, with x being ICA PSV or PSV ratio, the transformations $1/x$ and $1/x^2$ being motivated by visual inspection of the scatter plots. Note that no intercept was used since ACCmax tends to zero when increasing the degree of stenosis (i.e., corresponding to increasing values of ICA PSV or PSV ratio). For all analyses, the assumption was made that the velocimetric values in every vessel were independent. To investigate differences in ACCmax between categorical groups the Mann–Whitney U test was used (Fig. 4). In order to estimate the area under the curve (AUC) for the different parameters, ROC-curve analyses

were used. Bootstrap-analysis was used to evaluate confidence intervals for AUC ROC-curves of different parameters and Youden's index was used to determine the optimal cut-off value of a parameter. Differences with $P < 0.05$ were considered statistically significant. For all statistical analysis and graphics R (R Foundation for Statistical Computing, Vienna, Austria) was used.

Results

In total 676 patients underwent DUS of the carotid artery, which adds up to 2353 carotid artery measurements, as for some patients multiple DUS were performed during the study period. 1406 carotid arteries were excluded for several reasons mentioned in Figure 2, resulting in 947 carotid arteries available for analysis. From the group "post-surgical intervention (CEA)" in Figure 2, only three patients were excluded (485 carotid arteries) since the native contralateral side was not excluded after CEA. Repeated ICA measurements in the same patient were excluded in the last phase of the exclusion process, so every ICA was included only once.

The mean age of the study population was 67 years and 36% (198/545) of the patients were women. The majority of carotid arteries contained a <50% stenosis (75%, 710/947), followed by a ≥70%stenosis (14%, 128/947), and 50–69% stenosis (12%, 109/947), based on DUS as determined by Grant et al.[8.]

A Pearson correlation coefficient (r) of −0.69 was found between ACCmax and ICA PSV. The regression analysis using a nonlinear model shows a coefficient of determination (R^2) of 0.88 between ACCmax and ICA PSV. By comparing ACCmax to PSV ratio a similar Pearson correlation coefficient (r −0.63) and coefficient of determination (R^2 0.87) were established. Figure 3 shows the measured data, as well as the fitted regression line of the nonlinear model between ACCmax versus ICA PSV and ACCmax versus PSV ratio.

Figure 4 depicts the plotted ACCmax divided in groups based on degree of stenosis as measured using DUS. There are significant differences in ACCmax between the following groups: <50% versus 50–69% stenosis ($P < 0.001$) and 50-69% versus ≥70% stenosis ($P < 0.001$).

In order to investigate which DUS parameter (ACCmax, ICA PSV or PSV ratio) is the most accurate one, all parameters were compared to CTA. In this analysis, a total of 132 CTA-images were reviewed, which contained 182 carotid arteries. Sixteen CTA-images were excluded due to poor image quality, e.g., artefacts caused by movement or insufficient contrast, which included 25 carotid arteries (for some patients the contralateral side to a

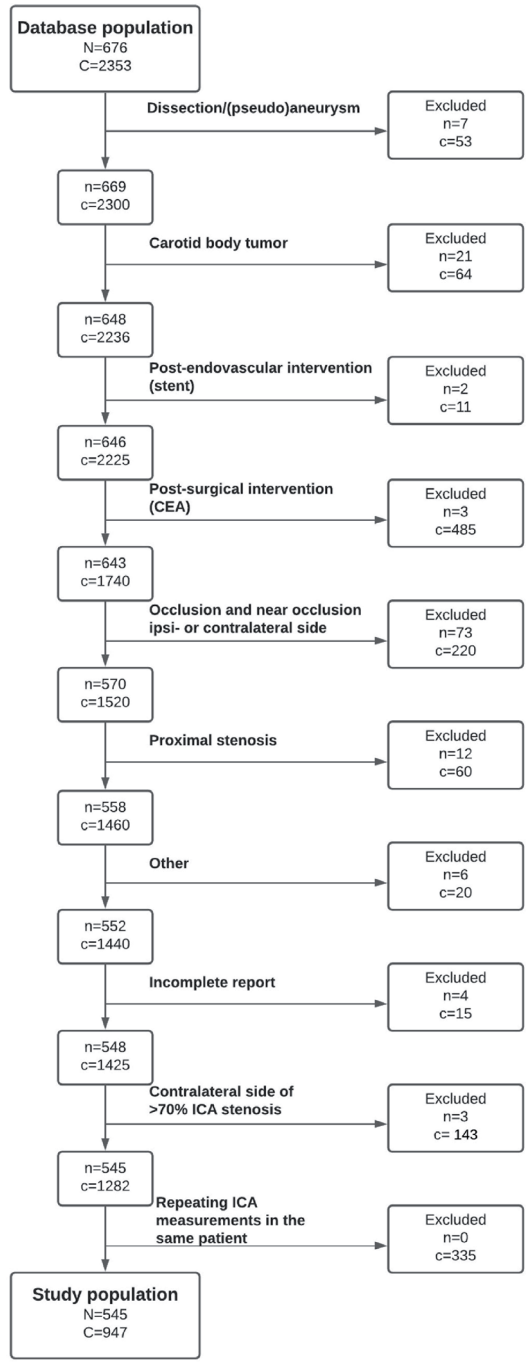

Fig. 2: Flowchart of the selection of patients. CEA = carotid endarterectomy; n = number of patients; c = number of carotid arteries; ICA = internal carotid artery. "Other" includes for example carotid-subclavian bypass. Repeating measurements in the same patient were excluded, so every ICA was included once.

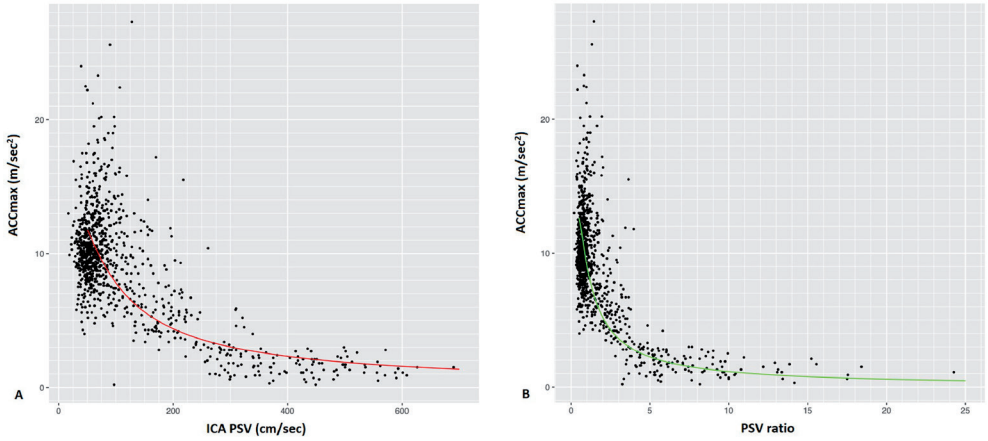

Fig. 3: Correlation between ACCmax vs. ICA PSV (A), and ACCmax versus PSV ratio (B). The scatterplot of 947 carotid arteries suggests a nonlinear relationship for both comparisons. For A, the line shows the data fitted by the nonlinear model: ACCmax ~ a/ICA PSV + b/ICA PSV^2. The fitted coefficients are a = 10.48 and b = -2.19. The coefficient of determination of this model is R^2 = .88. For B, the following nonlinear model was used: ACCmax ~ a/PSV ratio + b/PSV ratio^2. The fitted coefficients are a = 12.93 and b = -3.26. The coefficient of determination of this model is R^2 = .87. ACCmax: maximal systolic acceleration, ICA PSV: internal carotid artery peak systolic velocity, PSV ratio: peak systolic velocity ratio.

>70% ICA stenosis was already excluded by forming the study population, see Fig. 2). So, for this analysis 157 carotid arteries (116 patients) were enrolled. In this group 83 (53%) <50% ICA stenosis, 32 (20%) 50–69% ICA stenosis, and 42 (27%) ≥70% ICA stenosis was present.

Using ROC analysis, the area under the curves (AUC) for the different velocimetric parameters were calculated for detecting ≥70% and ≥50% stenosis, see Fig. 5, Fig. 6 respectively. Table I shows an overview of the performance characteristics of the cut-off values of ACCmax, ICA PSV and PSV ratio to diagnose a ≥70% and ≥50% ICA stenosis. For diagnosing a ≥70% ICA stenosis there were no significant differences in AUC between these parameters, calculated by bootstrap-analysis: AUC ACCmax versus AUC ICA PSV, $P = 0.05$; AUC ACCmax versus AUC PSV ratio, $P = 0.12$; and AUC PSV ratio versus AUC ICA PSV, $P = 0.76$. For diagnosing a ≥50% ICA stenosis there was a significant difference in AUC between ACCmax and PSV ratio ($P = 0.02$), and between ACCmax and ICA PSV ($P = 0.015$). The AUC between PSV ratio and ICA PSV was not significantly different ($P = 0.94$).

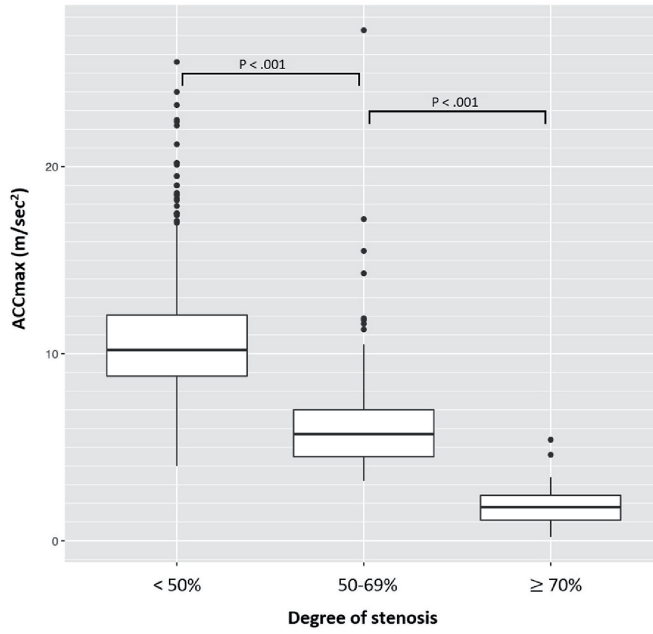

Fig. 4: ACCmax for different groups based on conventional DUS parameters. The study population (947 carotid arteries) were divided in different groups based on the criteria of Grant el al.7: <50%, 50–69%, and ≥70% stenosis but less than near occlusion. For each group the related ACCmax were given in boxplots (median, 25% quantile and 75% quantile are given). The significant differences in ACCmax between these groups are given in the figure and were determined with the Mann–Whitney U test.

	AUC (95% CI)	Optimal cut-off value	Sensitivity (%)	Specificity (%)	PLR	NLR
To diagnose ≥ 50% ICA stenosis						
ACCmax	0.88 (0.82-0.94)	7.15	82	88	6.83	0.20
ICA PSV	0.94 (0.91-0.97)	143	93	87	7.15	0.08
PSV ratio	0.94 (0.91-0.97)	1.77	88	89	8.00	0.13
To diagnose ≥ 70% ICA stenosis						
ACCmax	0.89 (0.82-0.95)	4.05	90	89	8.18	0.11
ICA PSV	0.94 (0.89-0.97)	212	86	90	8.60	0.16
PSV ratio	0.93 (0.89-0.97)	3.21	90	89	8.18	0.11

Table I: Diagnostic performance characteristics of DUS parameters to identify ICA stenosis compared to CTA as reference test
Optimal cut-off values were calculated using Youden's index
ACCmax, maximal systolic acceleration in m/sec^2; AUC, area under the curve; ICA PSV, internal carotid artery peak systolic velocity in cm/sec; NLR, negative likelihood ratio; PLR, Positive likelihood ratio; PSV ratio, ICA PSV / CCA PSV

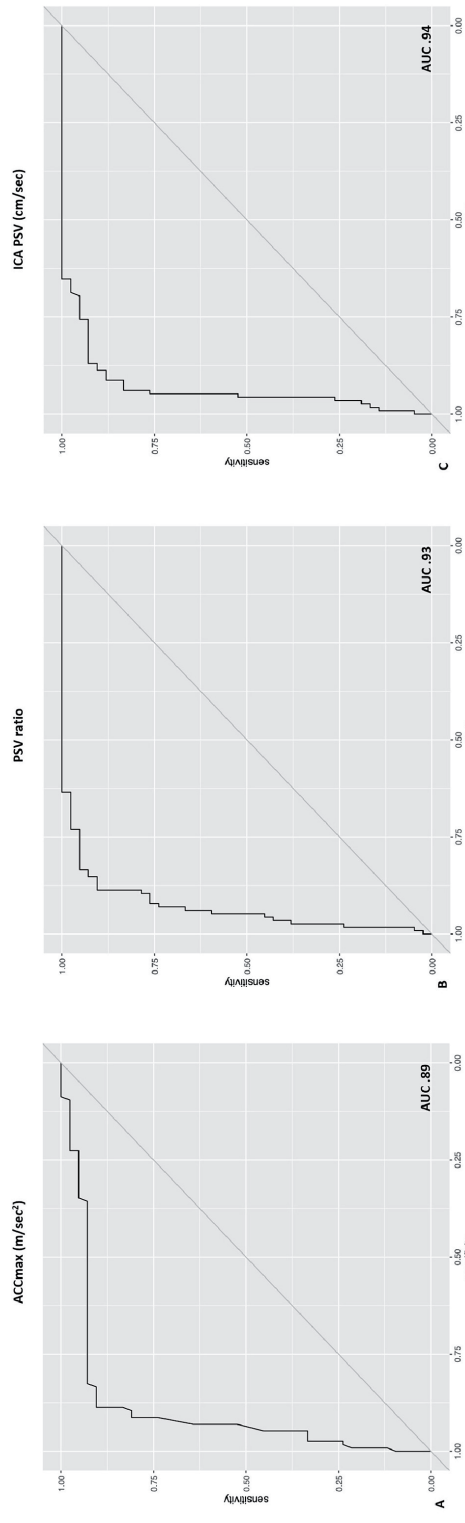

Fig. 5: ROC-curves for ACCmax, PSV ratio and ICA PSV for diagnosing ≥70% ICA stenosis. Data of 157 carotid arteries were used for determining the ROC-curves for ACCmax (A), PSV ratio (B) and ICA PSV (C) to diagnose ≥70% carotid stenosis (based on CTA-imaging). The area under the curve (AUC) is given in the figure. ACCmax: maximal systolic acceleration, PSV ratio: peak systolic velocity ratio, ICA PSV: internal carotid artery peak systolic velocity.

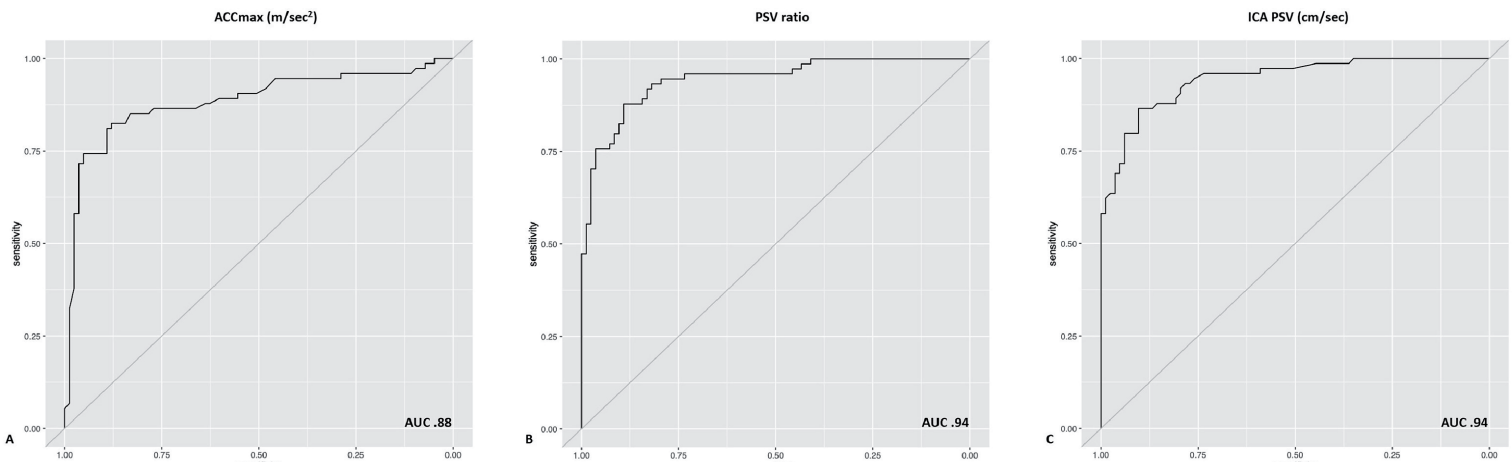

Fig. 6: ROC-curves for ACCmax, PSV ratio and ICA PSV for diagnosing ≥50% ICA stenosis. Data of 157 carotid arteries were used for determining the ROC-curves for ACCmax (A), PSV ratio (B) and ICA PSV (C) to diagnose ≥50% carotid stenosis (based on CTA-imaging). The area under the curve (AUC) is given in the figure. ACCmax: maximal systolic acceleration, PSV ratio: peak systolic velocity ratio, ICA PSV: internal carotid artery peak systolic velocity.

Discussion

The velocimetric DUS parameter ACCmax has a strong correlation with conventional velocimetric DUS parameters that are currently used in clinical practice – ICA PSV and PSV ratio – for quantification the degree of ICA stenosis. The ACCmax decreased as the severity of stenosis increased, and by using the ACCmax a distinction can be made concerning stenosis categories (<50%, 50–69%, ≥70%). ACCmax can be used to diagnose a ≥50% and ≥70% ICA stenosis based on the diagnostic performance characteristics as given in Table I. However, ACCmax was somewhat inferior to diagnose a simple ≥50% ICA stenosis as compared to conventional Duplex parameters ICA PSV and PSV ratio.

The benefit of ACCmax is not in the accuracy of detecting a simple mild ICA stenosis, but in the ability to perform the measurement at an additional measuring point to avoid the influence of local distorting factors of a plaque. Note that all four conventional DUS parameters (ICA PSV, optical estimation of the stenosis, PSV ratio (ICA/CCA), ICA EDV) according to the Society of Radiologists in Ultrasound Consensus Conference, relies on measurements at the level of the stenosis.[8] From literature it is known that in 6.5% of the ICA stenosis acoustic shadow obscures the vessel lumen and thereby severely inhibiting the ability to obtain conventional DUS measurements.[12] ACCmax is measured distally to the stenosis, providing opportunities to avoid local acoustic shadow of a calcified stenosis. Therefore, ACCmax could be useful in patients with carotid artery stenosis that hamper an accurate DUS measurement in the stenosis.

The European and American guidelines mention DUS measurements as initial screening for carotid artery stenosis.[6,7] Considering the critical role of DUS in the evaluation of carotid artery stenosis, it is important that it is reliable and accurate. Since it is not possible to accurately derive the absolute degree of stenosis with DUS, multiple DUS parameters are combined to divide carotid stenosis in categories (<50%, 50–69%, and ≥70% stenosis but less than near occlusion).[8] Several studies report about the performance of DUS measurements. For detection of ≥70% stenosis a sensitivity of 89% and specificity of 84% was found for DUS in a meta-analysis (based on DSA).[27] However, to diagnose a 50–69% stenosis results are different, there seems to be less research available for this category. Wardlaw et al. shows that DUS (sensitivity of 36% and specificity of 91%) is substantially less accurate to diagnose a 50–69% stenosis and questioned the validity of them, since available data for this category is sparse.[27] Also, Sabeti et al. shows only 45% agreement between DUS and angiography in the differentiation of stenosis of less than 70%.[28] In these studies the gold standard DSA was used as reference test. Since DSA is not a common practice anymore for this patient population, CTA was used as reference test in the present study.

Bardelli et al.[18] described the novel ACCmax in 2006 for detection of renal artery stenosis. Subsequently several clinical studies were published about the ACCmax in renal artery stenosis[17,19,20] and peripheral artery diseases of the lower extremity[15,16], however without investigating the interobserver agreement clinically. A previous in vitro study[14] revealed a good interobserver agreement for ACCmax (intraclass correlation coefficient of 0.99) and a good correlation between ACCmax and intra-arterial pressure gradient (R^2 0.937) was found. In the present study the first perceptions of the value of ACCmax in carotid artery atherosclerotic disease are presented. Because a new parameter is introduced, we focused on basic principles in a large group of ICA stenosis. Apart from complex clinical settings (such as proximal stenosis of the supra-aortic arteries, near occlusions or tandem lesions), this study investigates the value of ACCmax at solitary ICA stenosis, in which the conventional DUS parameters have been proven. From here, future ACCmax research can be initiated. Future research should focus on: 1. evaluating ACCmax results in a prospective design to determine the performance of the cut-off values and interobserver agreement, 2. potential benefits of ACCmax in specific subgroups such as patients with proximal stenosis (diagnosed by a decreased ACCmax in CCA) and extensive calcific shadowing of the ICA. Novel spectral imaging (dual-energy CT) can be used to allow a more accurate assessment of calcified ICA stenosis compared to conventional CTA.[29]

Limitations

This retrospective study has several limitations that warrant discussion. Most of the patients (75% of the carotid arteries) had a <50% stenosis and a substantial smaller number contained a 50–69% (12%) or a ≥70% (14%) stenosis. ACCmax was computer-based calculated and obtained at a single representative curve performed with DUS, as other DUS parameters were determined (PSV and EDV). Recently, Buschmann et al.[16] introduced a computer algorithm for ACCmax including several waveforms making the measurement more robust. Due to the retrospective design of the present study no interobserver analysis of ACCmax was possible to perform. However, a good interobserver agreement for ACCmax (at a single representative waveform) was revealed in a flow model study (ICC 0.99).[14] Bias could be introduced during the DUS measurement process, since one observer investigated several parameters. If one or more of these parameters seems suspicious, the observer is able to double check the other parameters, making the measurements more reliable clinically, but possibly interfering with the scientific method. Since DSA is nowadays not a common practice to determine the degree of a carotid artery, DUS parameters (including ACCmax) were compared to CTA-determined stenosis, instead of the historical gold standard: DSA. Finally, the number of extensive calcified plaques that hamper the ability to obtain a reliable DUS measurement in the ICA was unknown in this study population as a result of the retrospective design.

Conclusion

The new velocimetric DUS parameter, maximal systolic acceleration (ACCmax), is an interesting diagnostic parameter in carotid artery stenosis. The present study shows that ACCmax has a strong correlation with currently used DUS parameters in detecting an ICA stenosis and can divided ICA stenosis into categories (<50%, 50–69%, ≥70%). Therefore, ACCmax can be used as additional measurement. It is easy to obtain and does not have the disadvantages of the conventional DUS parameters of local distorting factors since it is measured distal to the stenosis. Although, in our patient group ACCmax was less accurate to diagnose a ≥50% ICA stenosis compared to ICA PSV and PSV ratio, it is worthwhile to further investigate the accuracy of ACCmax in a prospective design and in specific subgroups such as patients with extensive calcified plaques.

Acknowledgments

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Chapter 6

Imaging assessment of carotid artery stenosis varies in clinical practice

Full manuscript, based on *Brouwers JJWM et al. Imaging Assessment of Carotid Artery Stenosis Varies in Clinical Practice (Research letter). Eur J Vasc Endovasc Surg. 2020 Oct;60(4):632-633.*

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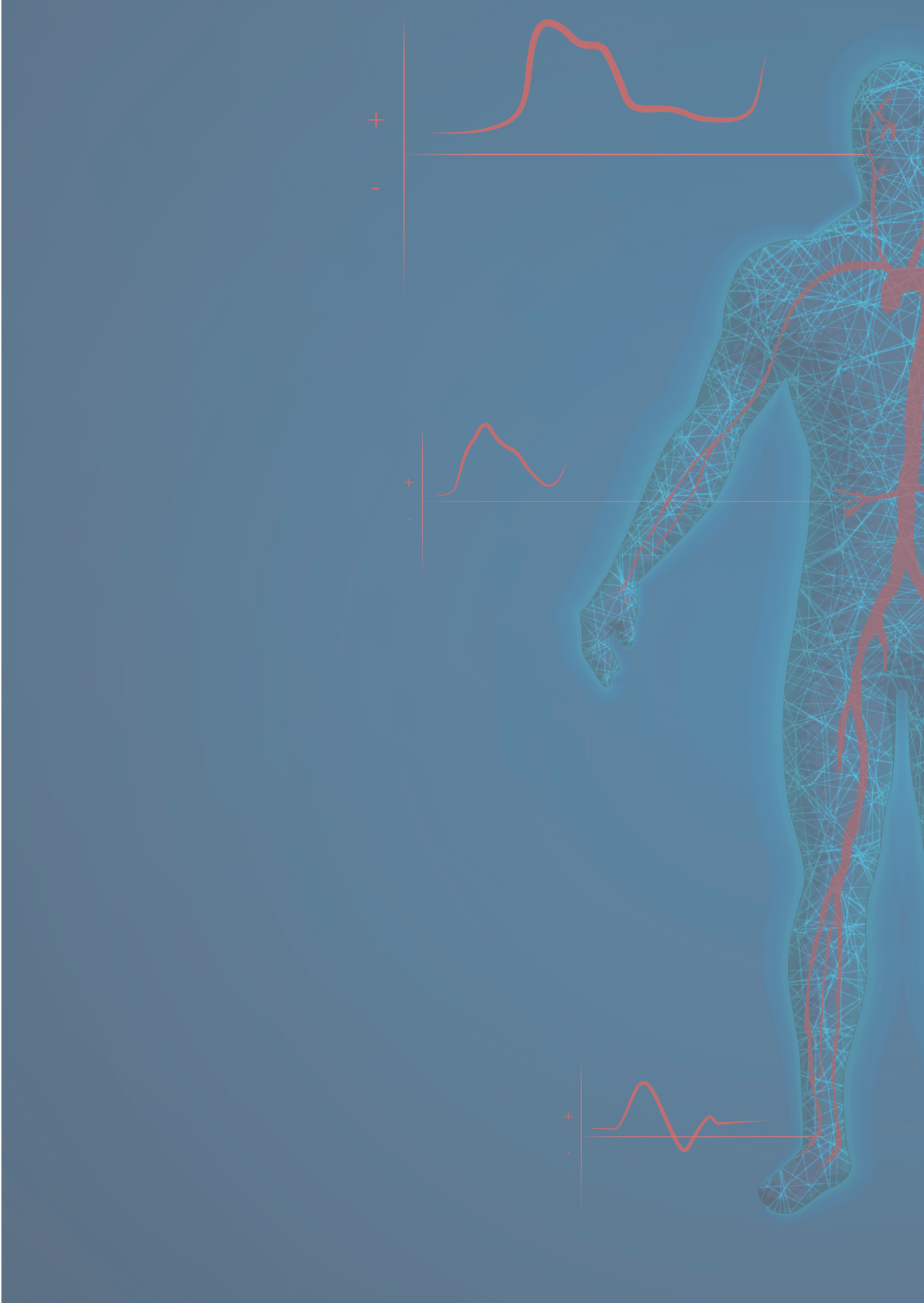

Background

According to current international guidelines, the degree of carotid artery stenosis should be determined by measuring the reduction in lumen diameter. The reduction in the cross-sectional area might provide a more accurate measure of carotid artery stenosis, particularly with irregularly shaped plaques, but it is not yet validated for use in clinical practice. The objective of this study was to determine which method, the diameter reduction method or the area reduction method, is generally used in current clinical practice.

Methods

Participants of the 2018 annual meeting of the European Society of Neuroradiology were approached for participation in this questionnaire-based study. The respondents were asked to indicate which method (reduction in diameter or area) they typically use to assess the degree of carotid artery stenosis according to different type of plaques. Furthermore, the questionnaire included questions regarding the clinical experience and the modalities used in practice.

Results

Ninety-two questionnaires were analyzed. For a regular/non-ulcerated and calcified plaque the diameter reduction was used most often to determine the degree of stenosis, respectively 67% and 62%. However, for an irregular/ulcerated plaque the use of the area reduction method as the sole method was 32%, and 13% used a combination of area and diameter reduction methods.

Conclusions

This study shows a variation in current practice concerning quantification methods of carotid artery stenosis according to the type of plaque. On CTA, the diameter reduction method is used most often to determine the degree of stenosis. Reduction in cross-sectional area for quantification of carotid artery stenosis is also used, in particular for irregular/ulcerated plaques. However, the area reduction method has not been validated for evaluation of patients' eligibility for carotid endarterectomy so far, and needs further evaluation before it can be implemented for use in clinical practice.

Abstract

Introduction

To date, the largest long-term trials with respect to the quantification, treatment, and outcome of carotid artery stenosis are the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST).[1,2] Using pooled data from these trials and reassessing the data obtained using the NASCET method, carotid endarterectomy (CEA) was found to be beneficial in neurologically symptomatic patients with a carotid artery diameter reduction of ≥50% on digital subtraction angiography (DSA), excluding patients with a near-occlusion.[3]

The diameter reduction method has therefore been established as the standard quantification method to assess the degree of carotid artery stenosis.[3–9] The diameter reduction method is nowadays being applied to computed tomography angiography (CTA) and magnetic resonance angiography (MRA) images.[7,8] However, diameter reduction method might not be optimal for assessment of carotid stenosis in arteries with irregular plaques.[7,8,10] Furthermore, a recent study showed that diameter-based measurements on CTA underestimate the degree of stenosis.[10] Alternatively, on CTA cross sectional area measurements can be performed; this method also considers the asymmetric shapes of a stenosis. Measuring the reduction in cross-sectional area might provide a more accurate estimate of the degree of stenosis, especially for irregular plaques. [6–8] However, evidence for using the cross-sectional area reduction method to select patients who should undergo CEA is lacking.[6,8–12]

In daily clinical practice, some radiologists already measure cross-sectional area reduction to estimate the degree of stenosis, but it is unclear to what extent this occurs. The objective of this study therefore was to determine which method – the diameter reduction method or the area reduction method – is generally used in current clinical practice to assess the degree of carotid artery stenosis.

Methods

Questionnaire and Respondents

The institutional review board approval was obtained to perform this study. For this study, radiologists and radiology residents from a wide range of countries (see Table 1) were approached at the 41st annual meeting of the European Society of Neuroradiology (ESNR) held in Rotterdam, the Netherlands in September 2018. To investigate which method radiologists generally use to quantify the degree of carotid artery stenosis, we generated a questionnaire (see Appendix 1). These questionnaires were made available for visitors to the congress. The respondents were asked whether they generally use the diameter reduction

	Respondents
Europe	**67 (73)**
Netherlands	16 (17)
Germany	7 (8)
Turkey	6 (7)
UK	6 (7)
Belgium	5 (5)
Switzerland	5 (5)
Asia	**8 (9)**
North America	**8 (9)**
Oceania	**5 (5)**
South America	**3 (3)**
Africa	**1 (1)**

Table 1: Countries in which the 92 respondents were located. Note that only the European countries with ≥5 respondents are listed separately. Data are presented as n (%).

method, which is the current standard for clinically evaluating carotid artery stenosis based on international guidelines.[1,2,12] Or whether they use the area reduction method, which is theoretically a more accurate method, particularly in cases with an irregular plaque. [6–8,10]

The questionnaire consisted of sixteen questions. Seven questions were directed to the respondents' background and clinical experience. The respondents were also asked to specify which diagnostic modalities they generally use in practice: echo duplex ultrasonography, computed tomography angiography (CTA), magnetic resonance angiography (MRA), digital subtraction angiography (DSA), or other. Furthermore, the respondents were asked to indicate which method (reduction in diameter or area) they typically use to assess the following type of plaque: 1. regular/non-ulcerated plaque; 2. irregular/ulcerated plaque; and 3. calcified plaque. The respondents who failed to answer all of the three questions regarding the type of plaque were excluded from our analysis. Data were collected and analyzed using SPSS Statistics version 25.0 (IBM Corp., Armonk, NY).

Results

A total of 93 respondents filled in the questionnaire. One respondent was excluded due to not answering questions in order to determine the used method regarding the type of plaque; thus, the results of 92 respondents (83 neuroradiologists, 8 neuroradiology residents, and 1 neurosurgeon) were included in the analysis. The average number of years of experience was 16 (range: 1- 35 years), and the majority (73%) of respondents is living in Europe (Table 1).

Most respondents (66%) are working in an academic tertiary referral hospital, followed by working in a non-academic teaching hospital (25%) and in a non-academic non-teaching hospital (8%). Four respondents (4%) reported that they work in two different hospital types, and one respondent did not answer.

Half of the respondents (49%) only use one modality to determine the degree of stenosis; the other half (51%) reported that they use two or more modalities (Table 2). The most commonly used modality was CTA, followed by echo duplex ultrasonography, MRA, and DSA.

The quantification methods used by the respondents to determine the degree of stenosis based on CTA are summarized in table 3. Diameter reduction method was used most often, in particular for regular/non-ulcerated plaques, followed by calcified plaques and irregular/ulcerated plaques, respectively 67%, 62% and 53%. However, for an irregular/ulcerated plaque the use of the area reduction method increased to 45% (use either the area reduction method exclusively or both the diameter reduction and area reduction methods). Furthermore, for an irregular/ulcerated plaque 32% used exclusively the area

	1 modality No. of respondents	**≥2 modalities** No. of respondents
Computed tomography angiography (CTA)	33 (36)	78 (85)
Echo duplex ultrasonography	8 (9)	39 (42)
Magnetic resonance angiography (MRA)	3 (3)	31 (34)
Digital subtraction angiography (DSA)	1 (1)	14 (15)
Other	0 (0)	0 (0)
Total	**45 (49)**	**162 (176)**

Table 2: Summary of the modality generally used by the 92 respondents to determine the degree of carotid artery stenosis. Data are presented as n (% of all respondents). The first column includes only the respondents who exclusively use one modality, whereas the second column includes also the 47 respondents who used more than one modality, resulting in a total of 176%. So, for example, in total 85% of the respondents used CTA, whether or not in combination with another modality.

Quantification method	Regular/non-ulcerated plaques	Irregular/ulcerated plaques	Calcified plaques
Diameter reduction	62 (67)	49 (53)	57 (62)
Area reduction	18 (20)	29 (32)	22 (24)
Both (diameter and area reduction)	11 (12)	12 (13)	9 (10)
No answer given	1 (1)	2 (2)	4 (4)
Total	**92 (100)**	**92 (100)**	**92 (100)**

Table 3: Overview of the quantification method used by the 92 respondents to determine the degree of carotid artery stenosis, according to each type of plaque. Data are presented as n (%).

reduction method, and this was 24% for calcified and 20% for regular/non-ulcerated plaques. Interestingly, overall, a total of 42 respondents (46%) reported that they use area reduction method—either exclusively or in addition to the diameter reduction method—for quantifying the degree of carotid artery stenosis.

Discussion

Our survey showed that the method used to assess degree of carotid artery stenosis (diameter or area reduction method) varies according to the type of plaque. The diameter reduction method is used most often for all plaque types, especially in regular/non-ulcerated and calcified plaques, respectively 67% and 62%. However, the cross-sectional area reduction method is also used to determine the degree of stenosis, in particular for irregular/ulcerated plaques. In these type of plaques the area reduction method was used in 45% (either using the area reduction method exclusively or using both the diameter reduction and area reduction methods). Moreover, for an irregular/ulcerated plaque the use of the area reduction method as the sole method was 32%. This result is remarkable, because current guidelines do not consider measuring area reduction to be the standard approach—or even an option—for determining the degree of stenosis.[1,2,9,12] Even though area reduction is suggested to be a more accurate method and theoretically might express the true hemodynamic significance of the lesion better than the diameter stenosis method, it is not validated for use in clinical practice.[7–10]

In a completely concentric stenosis, the reduction in lumen diameter can be directly translated to the reduction in cross-sectional area; for example, a 50% reduction in the lumen diameter translates to a 75% reduction in cross-sectional area.[6] However, atherosclerosis is usually an asymmetrical process.[6–8,10] In addition, a small change in the diameter of the carotid lumen can cause a much larger change in the lumen's cross-sectional area.[6,7] There is currently no consensus to what extent measuring diameter reduction differs from

measuring cross-sectional area reduction in a clinical setting.[6–11] Carnicelli et al. reported no significant overall difference between diameter reduction and area reduction due to carotid artery stenosis on CTA.[9] In contrast, Samarzija et al. argued that measuring area reduction is more accurate for assessing the degree of stenosis compared to measuring diameter reduction; the area reduction method had a higher predictive power for a correct stenosis classification with a better balanced sensitivity and specificity and significantly higher area under the ROC curve (AUC) value.[10] Moreover, they reported that the degree of stenosis can be significantly underestimated when using the diameter reduction method.[10] Zhang et al. found that in case of a non-circular stenosis, the reduction in area often provides a less-severe estimate of the resulting hemodynamic consequences compared to measuring the reduction in diameter. The authors concluded that measuring the reduction in diameter may not be ideal for determining the degree of stenosis, particularly in the case of a non-circular stenosis. Furthermore, they suggest that measuring the reduction in area may be more clinically relevant in terms of assessing the risk of stroke.[8] In addition, both Zhang et al. and Bartlett et al. found excellent intraobserver and interobserver reproducibility with respect to using the area reduction method for assessing the degree of stenosis[7,8], and Bucek et al. reported that interobserver reproducibility is higher with the area reduction method compared to diameter reduction.[11]

In an individual patient, it is clear that the degree of stenosis can vary widely depending on which method is used.[6–11] For example, Carnicelli et al. showed that degree of carotid artery stenosis can be either <40% and > 80% or > 50% and < 20% when determined by diameter reduction and area reduction, respectively.[9] In symptomatic patients with ≥50% stenosis measured based on the diameter reduction method, CEA is generally more effective than medical therapy in reducing the risk of stroke.[1,2,8] It is possible that some patients may undergo CEA unnecessarily due to the variability in measurements between the diameter and area reduction. Also, conversely, some patients might be deprived of CEA unnecessarily. Therefore, determining the appropriate treatment requires an accurate and consistent determination of the degree of stenosis.

This questionnaire based survey shows that the preference for one method over the other varies according to plaque type in current clinical practice, and includes measurement of area reduction, a method that has not been validated to identify patients who might benefit from CEA after an ischemic event. Following the results of two large long-term trials (NASCET and ECST), the current guidelines call for measuring the reduction in lumen diameter to select patients for CEA.[1,2,12] In our opinion, area reduction measurement should be the preferred method to determine the degree of stenosis as there is evidence that this method is more accurate than the diameter reduction method, in particular for irregular plaques. However, firstly, consensus should be reached if measurement of cross sectional area reduction differs from measurement of diameter reduction in a clinical setting. If

consensus is reached that the degree of stenosis is generally different between the diameter and area reduction method, future studies must show whether new cutoff values should be determined when using the area reduction method to identify patients that will benefit from CEA.

Limitations

The questionnaires were completed by participant of an international congress, in which the response rate was unknown which introduces the possibility of response bias and selection bias. So, the percentages generated in this survey must be considered with caution. Secondly, the majority of respondents (73%) were practicing in Europe and 17% came from the Netherlands, which might result in selection bias. Lastly, with respect to table 2, it is not clear to what extent the respondents (especially radiologist) knew about the used modalities for the work-up of a carotid artery stenosis that was done by a vascular surgery or neurologist. So, care must be taken in the interpretation of this table.

Conclusion

The quantification method of carotid artery stenosis on CTA seems to vary according to the type of plaque. The diameter reduction method is used most often, especially for a regular/non-ulcerated and calcified plaque. However, the area reduction method is also used, in particular for irregular/ulcerated plaques. To select patients for CEA the area reduction method should be used with caution, because the relation between the results of cross-sectional area reduction and diameter reduction measurement is still unclear. Although the area reduction method seems promising, there is currently no evidence for using this method to select patients for CEA and this method needs validation before it can be implemented for use in clinical practice.

Acknowledgements

The authors thank the European Society of Neuroradiology (ESNR) for enabling us to circulate our questionnaire to specialists from all over the world at the 41st annual meeting.

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Appendix 1: Carotid Artery Stenosis Questionnaire

We are currently investigating the radiologists' interpretation of carotid artery stenosis. We would highly appreciate your help in this important study by completion of the following questionnaire. All information is kept confidentially and anonymized. Thank you so much for your time in advance!

1. What is your nationality?_____

2. What is your gender?_____

3. Profession: o Radiologist o Radiology Resident

4. Years of experience (including period of resident)? _____

5. Country of residency training? _____

6. In which country are you currently working?_____

7. Do you work: o Academic (tertiary) o Non-academic training-hospital

o Non-academic non-training hospital

8. Which modality do you normally use to determine the degree of a carotid artery stenosis?

o Echo duplex ultrasonography o Computed Tomography Angiography (CTA)

o Magnetic Resonance Angiography (MRA) o Digital Subtraction Angiography (DSA)

o Other: _____

9. Is there a 3D CT reconstruction possible in your hospital for carotid artery stenosis?

o No

o Yes

10. Which plane/reconstruction do you use to determine the degree of carotid artery stenosis (on CTA)?

o Axial plane reconstruction o Sagittal plane reconstruction

o 3D CTA reconstruction

o Other: _____

11. What is your used method to determine the degree of carotid artery stenosis (on CTA) in case of a regular/non-ulcerated plaque?

o Calculation based on diameter reduction o Calculation based on area reduction

o Estimation based on diameter reduction o Estimation based on area reduction

o Other: _____

12. What is your used method to determine the degree of carotid artery stenosis (on CTA) in case of an irregular/ulcerated plaque?

o Calculation based on diameter reduction o Calculation based on area reduction
o Estimation based on diameter reduction o Estimation based on area reduction
o Other: _____

13. What is your used method to determine the degree of carotid artery stenosis (on CTA) in case of a calcified plaque?

o Calculation based on diameter reduction o Calculation based on area reduction
o Estimation based on diameter reduction o Estimation based on area reduction
o Other:_____

14. Do you use (multi-modality) advanced visualization software (e.g. Vital Vitrea) to determine the degree of carotid artery stenosis?

o No o Yes
o Other: _____

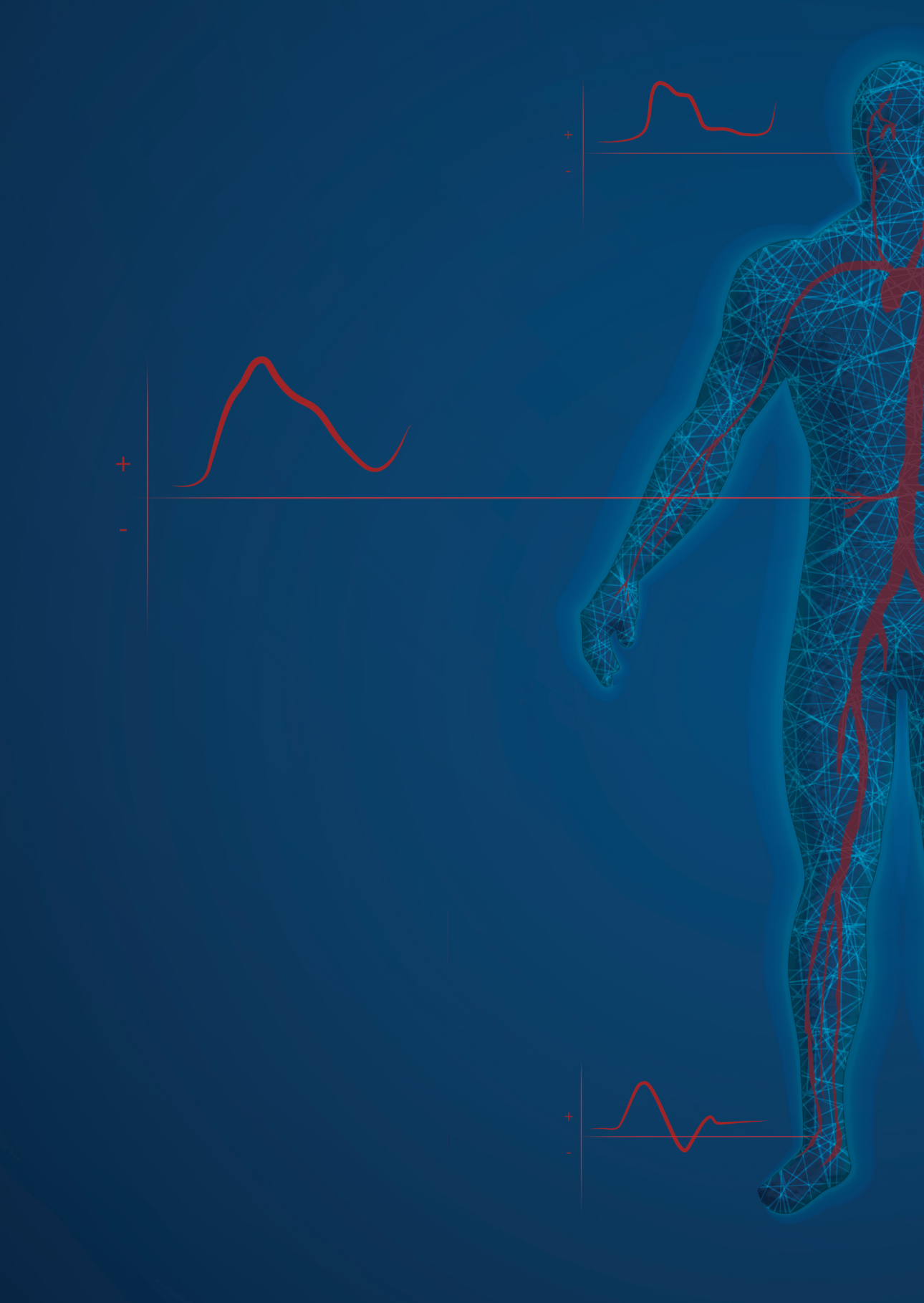
15. Fill in the dotted line.

50% diameter reduction corresponds to …… % area reduction in a full concentric carotid artery stenosis.

16 (last question). What made you decide to use diameter or area reduction to determine the degree of carotid artery stenosis (on CTA)? (you can write it down on the back)

Part III

Renal artery stenosis



Chapter 7

The use of intrarenal Doppler ultrasonography as predictor for positive outcome after renal artery revascularization

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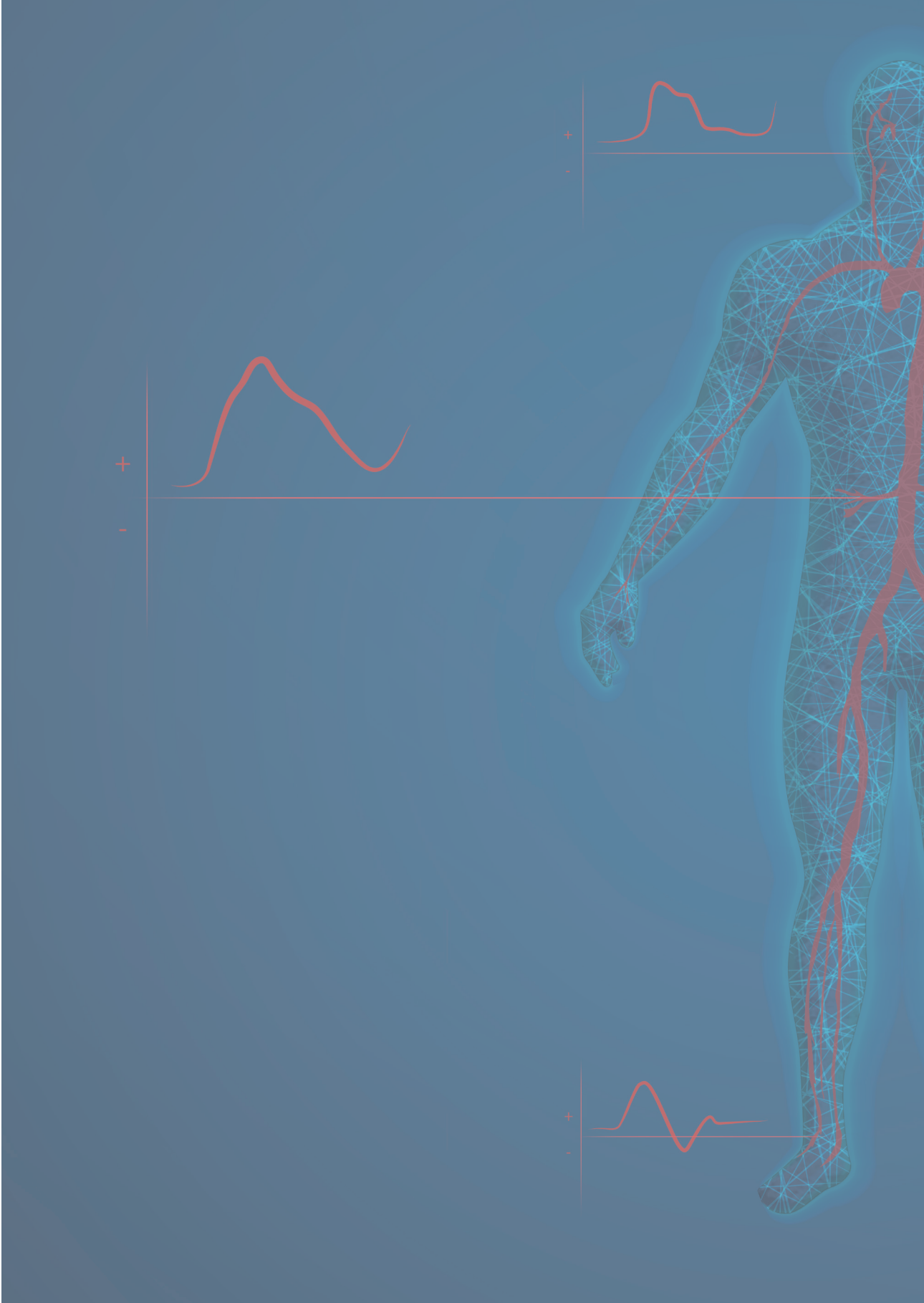

Background

Whether patients with renal artery stenosis should undergo therapeutic revascularization is controversial. In this retrospective study, we evaluated prognostic intrarenal Doppler ultrasound parameters that might have a predictive value for a beneficial response after renal revascularization.

Methods

From January 2003 until December 2012, all renovascular interventions for renal artery stenosis were analyzed. The resistive index and the maximal systolic acceleration were determined by Doppler ultrasonography prior to intervention.

Results

Thirty-two patients who underwent a renal revascularization procedure were included: 13 combined positive responders and 19 combined non-responders. The combined positive responders had a significant lower resistive index than the combined non-responders (0.5 vs. 0.6, $P = 0.001$) and a significant lower maximal systolic acceleration (1.0 vs. 3.8, $P = 0.001$) before revascularization. A prediction model ($RI \leq 0.5$ and $ACC_{max} \leq 1.3\ m/s^2$) was formulated to identify a subgroup that benefits from renal revascularization. This model has an expected sensitivity of 69% and specificity of 89% for improvement in renal function and/or blood pressure after revascularization.

Conclusion

The non-invasive intrarenal Doppler ultrasound parameters resistive index and maximal systolic acceleration can be used as tools to predict improvement in renal function and/or blood pressure after revascularization of renal artery stenosis. The clinical value of this prediction model should be evaluated in a prospective trial.

Abstract

Introduction

Renal artery stenosis (RAS) is a common cause of secondary hypertension and ischemic renal failure.[1] The prevalence of RAS is <1% in patients with mild to moderate hypertension.[2] But acute, severe or refractory hypertension and atherosclerosis elsewhere in the body highly increase the risk of RAS.[3–5] The primary cause of RAS is atherosclerosis (90%) that is associated with conventional cardiovascular risk factors such as age, diabetes, dyslipidemia and hyper- tension. Furthermore, atherosclerotic RAS is a progressive disease.[1,6] The second common cause of RAS is fibromuscular dysplasia (FMD), especially in young (female) adults.[7,8]

All patients with symptomatic RAS should receive medical treatment.[7] Whether patients with RAS should undergo therapeutic revascularization is far more controversial. Recent clinical trials such as the ASTRAL study,[9] STAR trial[10] and CORAL trial[11] found no significance difference in outcome (blood pressure, renal function and cardiovascular events) between revascularization plus medical therapy and medical therapy alone in patients with atherosclerotic renovascular disease. However, these studies did not close the debate on the value of revascularization therapy as a consequence of criticism concerning the design of these trials.[5,12,13] Furthermore, various observational studies showed beneficial outcome of revascularization compared to medical treatment in selected patients. This applies, for example, to patients presenting with flash pulmonary edema.[14–16] In addition, multiple case reports describe beneficial responses after renal revascularization therapy.[17–23] One can postulate that there must be a subgroup of patients with a symptomatic RAS who will benefit from revascularization. Therefore, identification of prognostic parameters for a positive response after revascularization might improve patient selection and efficacy of revascularization therapy in patients with RAS.

Currently, various diagnostic strategies are available to detect renovascular disease.[2] The intrarenal Doppler ultrasound parameter maximal systolic acceleration (ACCmax) emerged as a good non-invasive tool for diagnosing RAS with a sensitivity of 83%–94%.[24–26] Another ultrasound parameter is the resistive index (RI). The RI is a measure of pulsatile blood flow and is modified by vascular resistance and vascular compliance.[27] Increased RI is correlated with arteriolosclerosis, glomerulosclerosis and tubulointerstitial damage.[28] Previous studies revealed that a high RI correlates with no improvement in renal function and blood pressure after renal revascularization.[29–31] However, there is no consensus which patients will have a positive response in renal function and/or blood pressure from revascularization.

The objective of this study was to identify prognostic intrarenal Doppler ultrasonography parameters that might have a predictive value for a positive response from renal revascularization. Therefore, we performed a retrospective study in which we compared

patients who had a positive response from revascularization with patients who did not have such a response. We hypothesized that the RI and ACCmax might have prognostic value that could predict a positive response from revascularization in patients with RAS.

Methods

Study population

The institutional review board approved this retrospective study and waived the need for informed consent. Patients with uncontrolled hypertension (e.g., systolic blood pressure >150mmHg with two or more adequately dosed antihypertensive drugs) or unexplained renal dysfunction suggested a diagnosis of RAS. In these patients, renal arteries were visualized by digital subtraction angiography, magnetic resonance angiography or computed tomography angiography. A diameter stenosis of >70% was defined as a significant RAS. At our institution, the choice of treatment was made in consensus model during multidisciplinary conferences, in which vascular surgeons, nephrologists and interventional radiologists participate. Post-endovascular intervention patency was assessed directly after endovascular renal revascularization by angiography. After open surgery, all patients underwent Doppler ultrasonography and/or computed tomography angiography before discharge. An intraoperative complication and an occlusion or ≥10 mmHg post-stenotic pressure drop measured with a pressure wire in the renal artery directly after percutaneous revascularization were considered as a technically unsuccessful intervention.

All patients with endovascular and open renal revascularization between January 2003 and December 2012 were analyzed. In order to be included in this retrospective study, patients had to meet the following inclusion criteria: a reduction in the diameter of renal arteries of at least 70%, availability of laboratory data on renal function (estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease formula), mean arterial pressure (MAP) and Doppler ultrasonography parameters before intervention and availability of renal function and MAP six months after intervention. Technically unsuccessful revascularizations were excluded from this study.

Doppler ultrasonography

Since 2003, all intrarenal Doppler ultrasonography investigations were performed and well documented by the same vascular ultrasound specialist. The intrarenal Doppler ultrasonography parameters RI and ACCmax were performed using an Aloka SSD-5500 ultrasound system (Tokyo, Japan) with a 5–7.5MHz transducer in the period of 2003–2008 and an ACUSON S2000 model (Siemens Medical Solutions Inc., Ultrasound Division, Issaquah, WA) with a 4C1 3–4.5MHz Convex pro transducer in the period of 2008–2012.

The other intrarenal Doppler ultrasound findings were peak systolic velocity (PSV) and end- diastolic velocity (EDV). All the intrarenal Doppler ultrasonography findings were measured distal in the interlobar arteries in the upper, middle and lower renal pole. RI was calculated by the following formula: (PSV–EDV)/PSV. The ACCmax was defined as described by Bardelli et al.[24] and was always performed with angle correction[32] as shown in Figure 1. The extrarenal Doppler ultrasound findings were PSV of the abdominal aorta, and PSV and EDV measured at or directly after the stenosis.

Definition of responses to intervention

To determine the efficacy of revascularization therapy, renal function (eGFR) and MAP were determined before and six months after intervention. Other studies defined positive response in renal function as 20% increase in eGFR after intervention.[9,29,33] In our study, we defined an increase of ≥20% in eGFR and a decrease of ≥20% in MAP as positive responses, and these patients were classified as positive eGFR or MAP responders. Conversely, a decrease in eGFR of ≥20% or MAP increase of ≥20% was defined as negative responses.

The combined responses were established in Table 1, this is a combination of eGFR and MAP responses. A combined positive responder was defined as a minimum of at least one positive response and no negative response. This way we can compare the beneficial responders (combined positive responders) with the responders without benefit (combined non-responders). So, the combined responses were split in two groups: positive and non responders. And the eGFR and MAP responses were split in three groups: positive, non- and negative responders (Table 1).

		eGFR responses		
		positive (≥20% increase)	**Non-response (between 20% increase and 20% decrease)**	**negative (≥20% decrease)**
MAP responses	**positive (≥20% decrease)**	combined positive responder	combined positive responder	combined non-responder
	Non-response (between 20% decrease and 20% increase)	combined positive responder	combined non-responder	combined non-responder
	negative (≥20% increase)	combined non-responder	combined non-responder	combined non-responder

Table 1: Composite of the combined responders

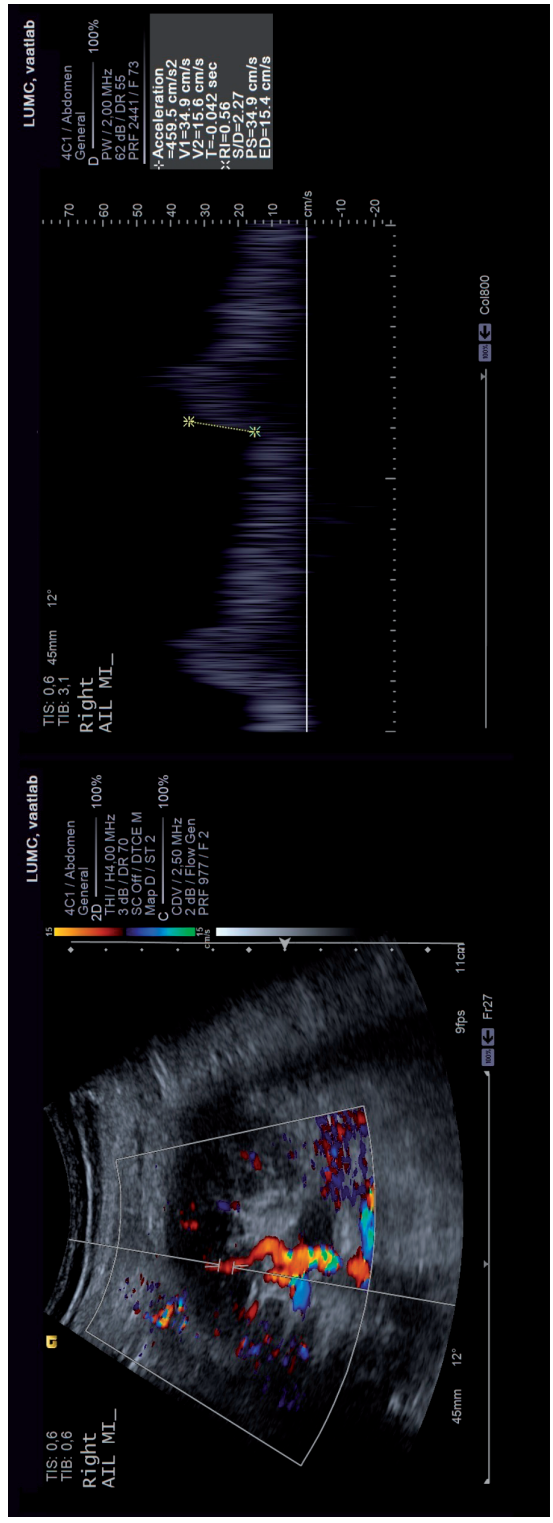

Figure 1: The RI (0.56) and ACCmax (0.46 m/s^2) were obtained by intrarenal Doppler ultrasonography. For measuring ACCmax, the angle of insonation will be close to null because the course of the interlobar artery is mostly perpendicular to the surface of the kidney. In this example, the angle of insonation is 12°.

Statistical analysis

Data were collected into a Microsoft Access database and were analyzed using SPSS statistics 20 and Matlab (R 2014A) for all statistical analysis. The Wilcoxon signed-rank test (Mann–Whitney test) was used as non-parametric test to assess continuous measures differences between groups because the study population is small and not all parameters were normally distributed (ACCmax). To ensure a homogeneous way of statistical analysis, the Wilcoxon signed-rank test (Mann–Whitney test) was used for all statistical ana- lyses where continuous measures differences between groups must be calculated. P values are given with median and interquartile range (IQR); 25th and 75th percentiles. The Chi-square test was used for analyzing two independent groups with categorical data. A P value <0.05 was considered statistically significant.

In this study, a prediction model was constructed, using a single cut-point on each variable (RI and ACCmax). To choose the cut-points, a grid of possible cut-points was defined for each variable by calculating percentiles from the observed values of RI and ACCmax in the data. For each combination of possible cut- points, classification performance was evaluated using a leave-one-out cross-validation procedure. We chose the model with minimal error rate among those models having a specificity of at least 80%. To obtain unbiased estimates of the error rates achievable with this model selection approach, the entire procedure was repeated using double cross-validation.[34,35]

Results

From January 2003 to December 2012, 104 interventions were identified for symptomatic RAS at our institution. Of the 104 revascularizations, 5 were excluded due to technically unsuccessful intervention (e.g., occlusion or ≥10 mmHg post-stenotic pressure drop immediately after intervention). Doppler ultra- sonography was not routinely performed for diagnosis of RAS, so we missed 54 RI and ACCmax data. Fortyfive interventions remained, whereof eGFR and MAP responses were identified. Thirteen eGFR or MAP data were missing, so 32 interventions were included and analyzed in this study (Figure 2).

Baseline characteristics

Baseline characteristics of the study population are shown in Table 2. Thirty-two revascularization interventions were included: 19 unilateral stenosis (1 re-stenosis), 2 bilateral stenoses/bilateral intervention and 11 solitary functioning kidney interventions (3 re-stenoses). Bilateral RAS was only once included in the study. The mean age in our study population was 58 years; 20 females and 12 males. The primary etiology of RAS was atherosclerosis (24/32) and second FMD (7/32). Sixteen percutaneous transluminal

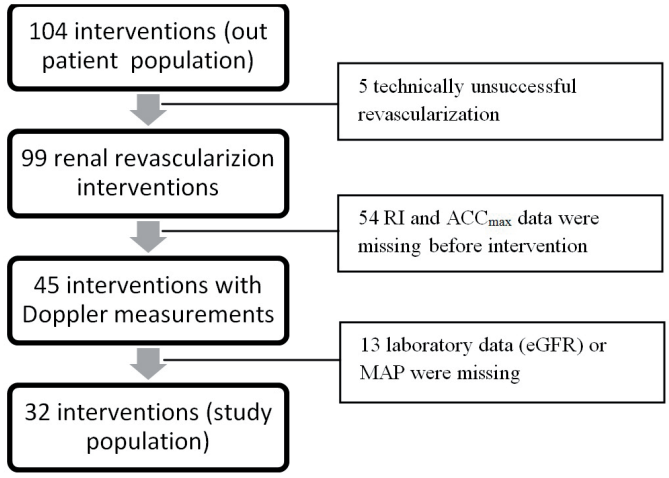

Figure 2: Flowchart of study selection.

angioplasty interventions without a stent, 6 percutaneous transluminal angioplasty interventions with a stent and 10 surgical revascularizations were done.

We classified 32 interventions in two groups, 13 interventions were included in the combined positive responders group and 19 interventions in the combined non-responders group, based on eGFR and/or MAP response (see "Definition of responses to intervention" section). These groups were compared to find parameters that are characteristic of the combined positive responders. The mean eGFR, serum creatinine, MAP, systolic blood pressure, diastolic blood pressure, RI, ACCmax and number of antihypertensive drugs before and six months after intervention for the two groups are given in Table 2. No significant differences were found in demographic parameters, type of intervention, laboratory measures, blood pressure or number of antihypertensive drugs.

Responses on intervention

The combined positive responders (13/32) had a significant lower median RI than the combined non-responders (0.5, 0.4–0.6 vs. 0.6, 0.6–0.7; P=0.001) and a significant lower median ACCmax (0.6, 0.5–1.3 vs. 2.1, 1.4–6.8; P=0.001) before intervention (Figures 3 and 4).

To answer the question of whether the RI and ACCmax were also predictive for renal function response alone, the eGFR responders were compared separately. The non- and negative eGFR responders were considered as one group because they both had no beneficial response in eGFR after revascularization. The positive eGFR responders (9/32) had a mean eGFR increase of 19 mL/min, and the non- and negative eGFR responders (23/32) had a mean decrease of 5mL/min in eGFR. The positive eGFR responders compared with

		Responders		
	Study population (N32)	**Combined positive responders (n=13)**	**Combined non-responders (n=19)**	**P value**
Demographic				
Age in years	58±13	55±13	60±13	0.291
Female	20 (63%)	6 (46%)	14 (74%)	0.114
Male	12 (38%)	7 (54%)	5 (26%)	0.114
Unilateral stenosis	19 (59%)	8 (62%)	11 (58%)	0.837
Left	4 (13%)	3 (23%)	1 (5%)	0.135
Right	15 (47%)	5 (39%)	10 (53%)	0.430
Bilateral stenosis	2 (6%)	2 (15%)	0 (0%)	0.077
Solitary functioning kidney	11 (34%)	3 (23%)	8 (42%)	0.266
Re-stenosis	4 (13%)	0 (0%)	4 (21%)	0.077
Atherosclerosis	24 (75%)	10 (77%)	14 (74%)	0.835
FMD	7 (22%)	2 (15%)	5 (26%)	0.463
Other cause[a]	1 (3%)	1 (8%)	0 (0%)	0.219
Interventions				
PTRA	16 (50%)	6 (46%)	10 (53%)	0.719
PTRA CIA (NTx)	2 (6%)	2 (15%)	0 (0%)	0.077
PTRAS AIE (NTx)	1 (3%)	1 (8%)	0 (0%)	0.219
PTRAS	5 (16%)	2 (15%)	3 (16%)	0.975
Aortorenal bypass	3 (9%)	1(8%)	2 (11%)	0.787
Hepatorenal bypass	3 (9%)	1(8%)	2 (11%)	0.787
Splenorenal bypass	1 (3%)	0 (0%)	1 (5%)	0.401
Revision splenorenal bypass	1 (3%)	0 (0%)	1 (5%)	0.401
Laboratory measures				
eGFR in ml/min (before intervention)	50±24	42±24	56±23	0.120
eGFR in ml/min (6 months after intervention)	52±23	54±23	50±23	0.687
Serum creatinine in µmul/L (before intervention)	148±78	178±79	128±88	0.024
Serum creatinine in µmul/L (6 months after intervention)	145±111	126±39	157±141	0.715
Blood pressure				
MAP in mmHg (before intervention)	115±15	113±16	116±14	0.552
MAP in mmHg (6 months after intervention)	101±13	98±14	103±12	0.539
Systolic blood pressure in mmHg (before intervention)	165±27	159±25	169±29	0.299
Systolic blood pressure in mmHg (6 months after intervention)	142±23	139±23	144±23	0.441

		Responders		
	Study population (N32)	**Combined positive responders (n=13)**	**Combined non-responders (n=19)**	**P value**
Diastolic blood pressure in mmHg (before intervention)	90±13	90±13	90±14	0.985
Diastolic blood pressure in mmHg (6 months after intervention)	81±11	78±12	82±11	0.642
Intrarenal Doppler ultrasonography (side with stenosis)				
Resistive Index (RI)	0.6±0.1	0.5±0.1	0.6±0.1	0.001
Median RI Maximal systolic acceleration (ACC_{max}) in m/sec^2 Median ACC_{max} in m/sec^2	0.6 (0.5-0.7) 2.7±3.1 1.7 (0.6-2.7)	0.5 (0.4-0.6) 1.0±0.8 0.6 (0.5-1.3)	0.6 (0.6-0.7) 3.8±3.6 2.1 (1.4-6.8)	0.001 0.001 0.001
Number of antihypertensive drugs				
Before intervention	3±1.2 (n26)	3±1.0 (n11)	2±1.3 (n15)	0.572
6 months after intervention	2±1.4 (n22)	2±1.4 (n9)	3±1.4 (n13)	0.538

Table 2: Baseline characteristics
AIE = external iliac artery, CIA= common iliac artery, eGFR= estimated Glomerular Filtration Rate, MAP= mean arterial pressure, NTx= Renal transplant recipients, PTRA= percutaneous transluminal angioplasty interventions without a stent, PTRAS= percutaneous transluminal angioplasty interventions with a stent.
[a]Iatrogenic stenosis due to a hemorrhaging complication of nephrectomy for Grawitz tumor. P value were calculated with use of the Wilcoxon signed-rank test (Mann-Whitney test) or the Chi-Square test. Data are mean±standard deviation (SD), median (IQR) or n (%). SD or IQR for continuous factors and frequency (%) for dichotomous factors.

the non- and negative eGFR responders showed a significant lower median RI (0.4, 0.4–0.6 vs. 0.6, 0.5–0.7; P 1⁄4 0.002) and a significant lower median ACCmax (0.6, 0.4–0.7 vs. 2.1, 1.2–4.2; P < 0.001) (Figures 3 and 4). A separate comparison between MAP responders was useless because 9 (of the 32) patients had a normal MAP at baseline.

Prediction model based on RI and ACCmax

A prediction model was formulated to identify a subgroup prior to intervention that will have a positive response from renal revascularization. The leave- one-out cross-validation procedure was used to determine the optimal cut-off values of RI and ACCmax, for classification of future patients. The best cut-off values for RI and ACCmax were respectively found at 0.5 and 1.3 m/s^2. The prediction model classifies patients as expected positive responders if the patient scored at or below the respective cut-off points on both variables.

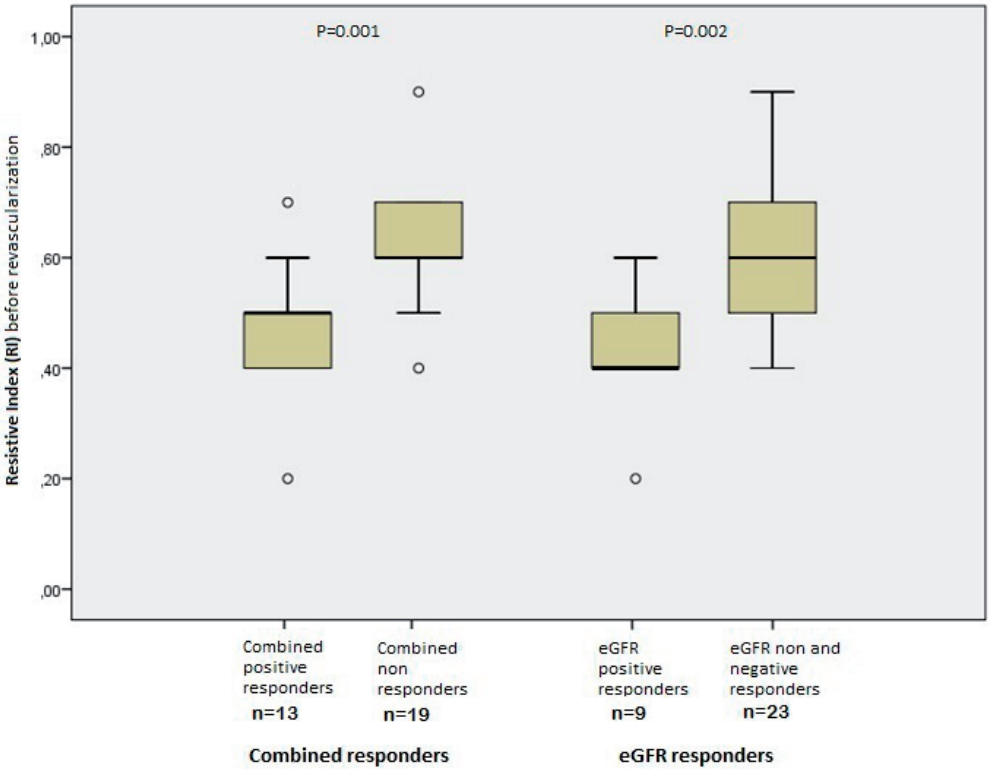

Figure 3: Significant difference in resistive index (RI) before intervention between combined responders (P=0.001) and eGFR responders (P=0.002). Median and the highest and the lowest case within the IQR and 1.5 IQR (top and bottom whiskers) are given in the figure. Outliers are identified with an o.

The performance of this prediction model was calculated by double cross-validation (see Tables 3 and 4). This statistical analysis estimates an expected sensitivity of 69% and specificity of 89% for a positive response after renal revascularization for application of the above-described rule on new patient observations (total double-cross-validated error rate was 6/32). The combination of individual intrarenal Doppler ultrasonography data (RI and ACCmax) of our study population and the unbiased calculated cut-off values are demonstrated in Figure 5.

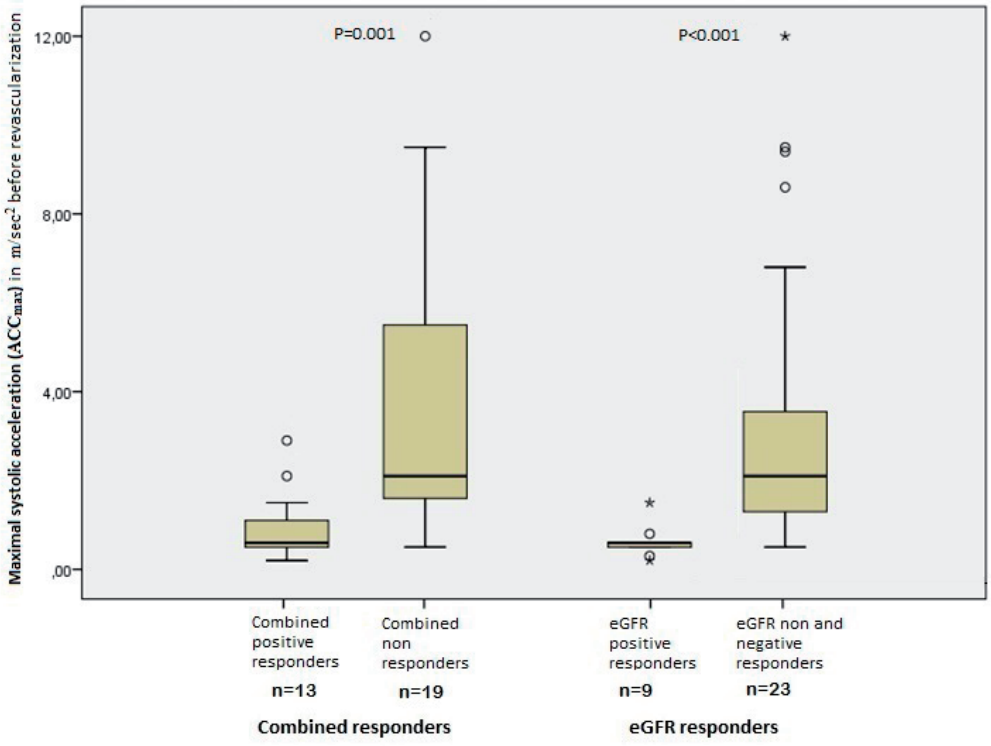

Figure 4: Significant difference in maximal systolic acceleration (ACCmax) before intervention between combined responders (P=0.001) and eGFR responders (P < 0.001). Median and the highest and the lowest case within the IQR and 1.5 IQR (top and bottom whiskers) are given in the figure. Outliers are identified with an o, and extreme values are marked with an asterisk (*).

	Expected positive response (based on prediction model)	Expected non-response (no intervention advise based on prediction model)	Total
Combined positive responders	9	4	13
Combined non-responders	2	17	19
Total	11	21	32

Table 3: Confusion table; combined responders and expected outcome.

Sensitivity	69%
Specificity	89%
Positive predictive value	82%
Negative predictive value	81%

Table 4: Expected statistical characteristics of the prediction model (based on double- cross-validation computation).

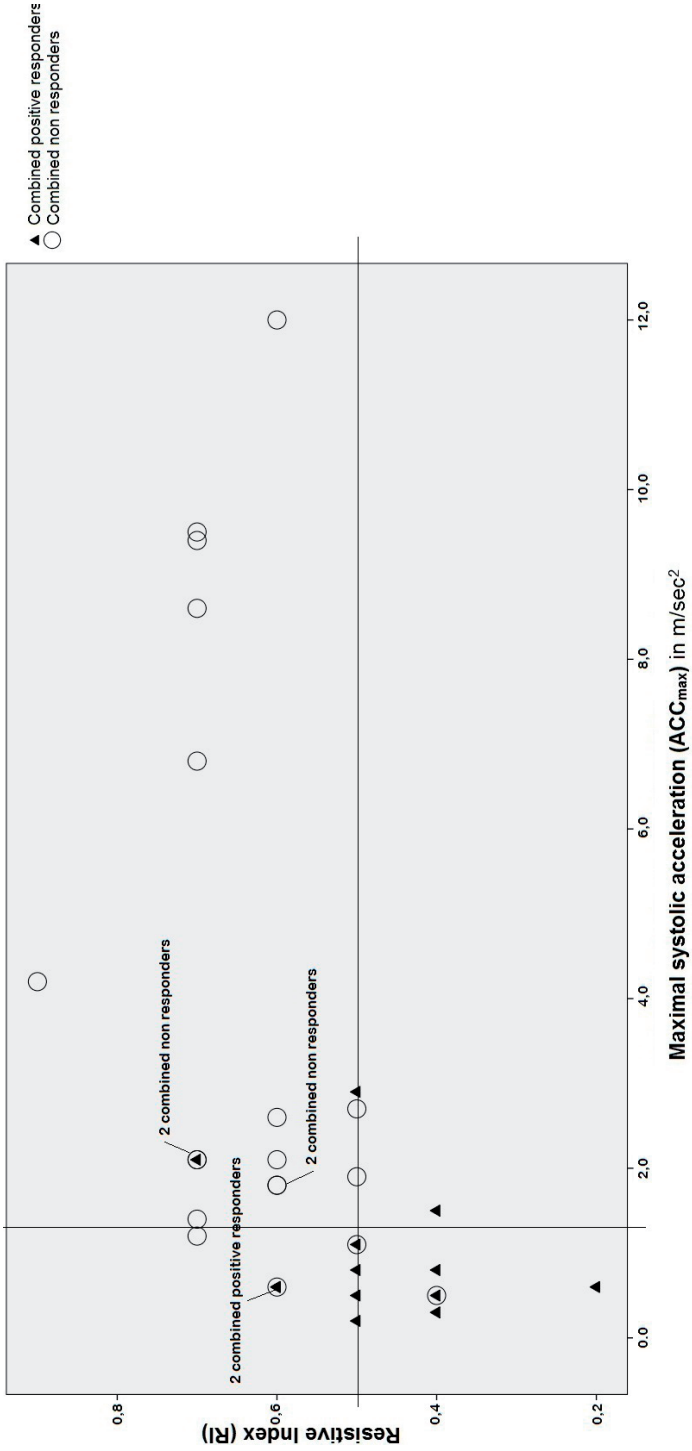

Figure 5: Scatterplot of the RI and ACCmax with the cut-off values, respectively, 0.5 and 1.3 m/s^2, from the total study population of 32 patients. Every symbol represents one patient. Readers should beware that the figure shows the observed patient measures with the chosen prediction model superimposed. Hence, the observed spread of observations in the figure is not directly comparable with the unbiased double cross-validatory estimates of classification performance (Tables 3 and 4) on future patients given in the text. A naïve comparison of patients with the thresholds shown would induce an optimistically biased assessment of classification performance.

Discussion

Theoretically, renal revascularization might improve renal function and blood pressure control in patients with RAS. However, technically successful renal artery revascularization does not guarantee positive responses in terms of blood pressure regulation, preservation of renal function and reduction of cardiovascular events. Recent clinical trials[9–11] showed a limited role for renal revascularization. As a result of criticism[5,12,13] concerning the design of these trials and various observational studies[14–16] showing beneficial outcome of renal revascularization compared to medical treatment in selected patients, one can postulate that there could be a subgroup of patients with a symptomatic RAS who will benefit from revascularization. The aim of this study is to identify parameters by intrarenal Doppler ultrasonography that is predictive for a positive response from revascularization.

The intrarenal Doppler ultrasonography is not only a tool to diagnose RAS,[24–26,36–39] but prior research has shown its usefulness in predicting patients to be excluded from revascularization.[29–31,40] To date, no valid and reliable selection methods are available to select patients who will have a positive response from renal revascularization. In our study, we postulate a prediction model (RI ≤ 0.5 and ACCmax ≤ 1.3 m/s^2) that enables selection of patients who have the potential to benefits from renal revascularization. For our prediction model, we would expect a sensitivity of 69% and a specificity of 89% for improvement in renal function and/or blood pressure when applied to new patients based on double-cross-validation computation.

The prediction model is a new objective instrument which has a contributing role in making a decision in the therapy of RAS. We prioritized the selection of patients who have a very high chance to have a beneficial response after renal revascularization, which limited the sensitivity of our model.

Schwerk et al.[36] introduced the RI as an indirect parameter for diagnosis and grading RAS. But more important is the predictive value of RI. According to Radermacher et al.,[30,41] high RI (≥0.8) is a predictor for a response without improvement in renal function, blood pressure or kidney survival after intervention for RAS. A retrospective study showed patients with RAS who underwent percutaneous intervention with RI < 0.8 had a significant better eGFR response than patients with RI ≥0.8.[29] Santos et al.[31] found a high RI (≥0.80) as the most powerful predictor for no improvement in blood pressure outcome (OR 99.6). Voiculescu et al.[40] suggested an RI ≥0.55 and negative rennin ratio for predicting poor outcome concerning blood pressure response for unilateral RAS with a sensitivity of 88% and specificity of 67%. To date, studies only exclude patients for revascularization; e.g., patients with a high RI. In our study, we observed a significant association between beneficial response and a low RI. A similar result was found in the study of Radermacher et al.[30] We obtained the Doppler

signals from interlobar arteries, and only Voiculescu et al.[40] measured the RI at the same position. Investigators in the other studies[29–31,36,41] measured the RI from segmental arteries. So measurements from the interlobar artery could be an explanation why Voiculescu et al.[40] and our study had a lower RI cut-off value than the other studies.

Bardelli et al.[24] found the best ACCmax cut off at 4.0 m/s^2 for diagnosing RAS with a sensitivity of 94% and negative predictive value (NPV) of 97%. Johansson et al.[26] used an acceleration of the blood flow <2.3 m/s^2 as a criterion for RAS with a sensitivity of 83% and NPV of 96%. And Saeed et al.[25] established the best ACCmax cut off at 3.80 m/s^2 with a sensitivity of 85% and NPV of 90% to diagnose RAS. To our knowledge, no study published an association between ACCmax and renal revascularization outcome. In our research, a low ACCmax correlates with a positive response in renal function and/or blood pressure after revascularization. The combined positive responders had a mean ACCmax of 1.0 m/s^2. The morphology of the Doppler spectrum waveform may result in biasing factors on Doppler measures. It is important to note that the ACCmax occurs at the inflection point where the upstroke changes from concave up to con- cave down. It is equal to the slope of the tangent line on the curve at the inflection point. This results in less biasing factors caused by morphology of the Doppler spectrum waveform.[24]

Due to multiple leading randomized controlled trials,[9–11] there are still only a few renal revascularizations performed nowadays. It is important to minimize the number of unnecessary interventions, so the selection criteria must be very strict. Consequently, a minimal expected specificity of 80% was required to calculate the cut-off points of our prediction model. These cut-off points were calculated based on a singlelevel leave-one-out cross-validatory assessment across a range of potential cut-points. Because the statistical analysis for calculating the cut-off points involves an evaluation across all patients and our total sample size is small, some care must be applied when comparing the observed patient data with the thus chosen cut-off points. This would lead to a biased assessment and statement of predictive ability on future patients. To avoid this problem, the entire classification procedure was repeated using a double-cross-validatory procedure, as described in Mertens et al.[35] See also Figure 5, which shows the raw patient data superimposed on the optimized grid of cut-off points chosen by the single-cross-validation approach. In this figure, there were two patients who undergo revascularization without a combined positive response. If we look at these patients, they did have a decrease of 8% and 18% in MAP; but in our study, they were both MAP non-responders (see "Definition of responses to intervention" section). Additionally, they had respectively a normal and a slightly reduced eGFR at baseline.

De Leeuw et al.[13] described that the selection of patients is not optimal in angioplasty trials, such as in the ASTRAL trial.[9] The poor outcome from angioplasty is explicable by the

pathophysiological principles. Generally, patients with already irreversible renal damage from RAS, so with less viable kidney tissue left, were included in the trial. Consequently, these patients have poor chances of beneficial response after intervention.[13] Santos et al.[31] suggested the poor outcome of renal artery revascularization might be explainable with the increased vascular resistance in the renal parenchyma due to glomerulosclerosis from longstanding hypertension. Ikee et al.[28] concluded an increase of RI is associated with renal histopathologic characteristics, particularly arteriolosclerosis. In our study, the non-responders had higher mean RI (0.63) compared to the positive responders (0.48). So there are indications that it is possible to select patients who have potential to improve after revascularization by using the intrarenal Doppler ultrasound. Furthermore, intrarenal Doppler ultrasonography is low cost, widely available, a non-invasive measurement and suitable for patients who cannot undergo angiography. In addition, the Doppler ultrasonography equipment is strongly improved in resolution in course of time. Consequently, the intrarenal RI and ACCmax are now well reproducible and very reliable in contrast to the past.

Limitations

In our study, all patients were treated in the same hospital. Consequently, percutaneous transluminal angioplasty interventions without a stent, percutaneous transluminal angioplasty interventions with a stent and open surgery revascularization were done by a small group of specialists. Although we found interesting findings in this study, there are several limitations. Due to the retrospective design of the study, multiple patients with renal artery revascularization were excluded from the analysis based on missing clinical data. In part, this relates to the absence of the Doppler parameters RI and ACCmax in a proportion of patients, as these parameters were not included in the routine work up during the entire study period. A sample selection-bias might have occurred through the inclusion and exclusion criteria of this study, e.g., all technically unsuccessful interventions (5 of the 104 patients) and patients with missing essential clinical data were excluded. However, we assume that the included patients do represent the total cohort of patients, as missing data were aselectively distributed. In additional, we had a small cohort of mixed composition including FMD and re-stenosis. Re-stenosis is generally known as a complication after revascularization and should therefore be included in the study population.

Conclusion

Technically successful renal artery revascularization does not guarantee positive responses in terms of blood pressure regulation and preservation of renal function. We postulate that our prediction model (RI ≤ 0.5 and ACCmax ≤ 1.3 m/s2), based on intrarenal Doppler ultrasonography, is a non-invasive tool to select RAS patients who have the potential to benefit from renal revascularization. This prediction model might be promising although it should be evaluated in a larger prospective study population to ensure its validity.

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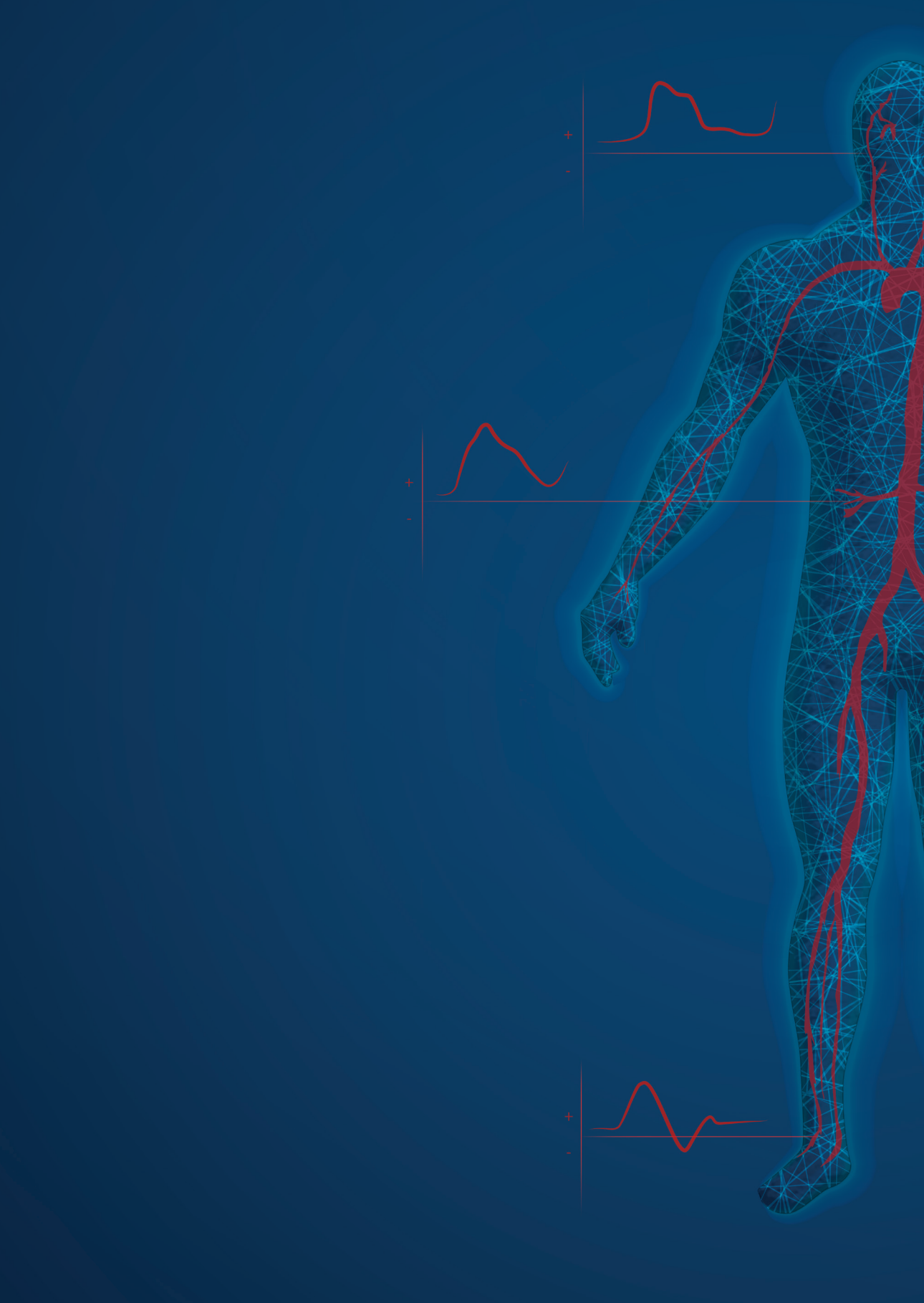
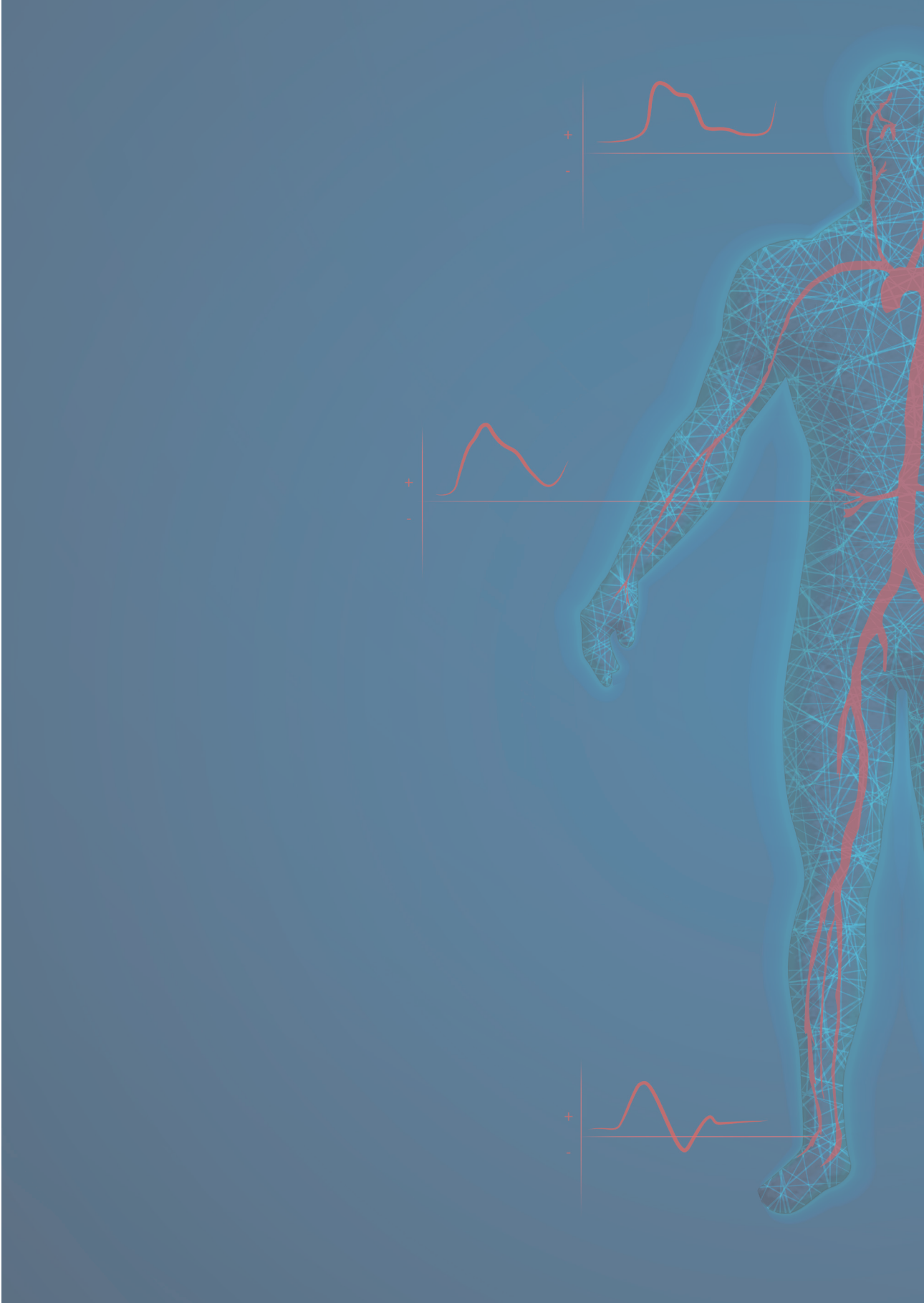
Part IV

General discussion, future perspectives, summary and appendices



Chapter 8

General discussion and future perspectives



Non-invasive diagnostics are the first-line tools to diagnose an atherosclerotic vascular disease (carotid artery, renal artery and lower extremity). The accuracy of these non-invasive measurements is of utmost importance since it could have drastic consequences. In patients with diabetic foot ulcers (DFU), timely recognition of PAD and treatment (if necessary) is essential to increase the chance of wound healing.[1,2] In carotid artery stenosis reliable DUS measurements can rule in or rule out a significant stenosis, and is one of the key factors in decision making. Patients with renal artery stenosis (RAS) often also suffering from CKD, making CTA less appropriate. Therefore, accurate non-invasive diagnostics can make CTA unnecessary, and might select patients who will benefit from revascularization. We want to emphasize that in all atherosclerotic vascular diseases constant development of non-invasive measurements is crucial to improve our healthcare.

Peripheral arterial disease of the lower extremity

In the lower extremity, non-invasive diagnostics (bedside tests) to detect PAD are accurate in patients without MAC.[3] However, in patients with DM or CKD medial arterial calcification (MAC) can occur leading to false ABI, TP and TBI results. Particular in this vulnerable group of patients, early identification of PAD is essential to promptly start cardiovascular risk management (CVRM) and thus reduce the risk of events.[4] Also early revascularization in patients with critical limb ischemia is important to decrease complications and minimize morbidity.[1,2] Although it is well known that MAC hampers the performance of bedside tests to diagnose PAD, only 23 studies investigated the performance of bedside tests in patients prone to MAC (chapter 2 shows an overview in a systematic review).

When using the ABI (and excluding patients with ABI >1.3 in accordance with the international guidelines)[3,5] a reasonable performance was found to diagnose PAD (PLR 8.72-17).[6,7] However, ABI is insufficient to rule out PAD. Continuous waveform Doppler (CWD) device showed the best test performance to rule out PAD (NLR 0-0.28), but the definition of an abnormal CWD test is not consistent in literature. A monophasic or dampened waveform can be used for diagnosing PAD, while a loss of a triphasic pattern is also described as abnormal. When a loss of a triphasic pattern is used, PAD can be accurately ruled out (NLR 0-0.09). However, in most patients prone to MAC a dampened, monophasic, or biphasic waveform is found. Hence, the "threshold" loss of triphasic signal as a criterion for PAD will be of limited value in clinical practice. Toe pressure (TP) is often used in patients with ABI >1.3 since digital arteries are less affected by MAC. Remarkable, only three studies investigated the absolute TP to diagnose PAD in patients prone to MAC. Furthermore, even more remarkably, each study used a different threshold. A threshold of <50 mmHg showed an accurate performance to diagnose PAD, but a poor performance to rule out PAD was found.[8] In the other two studies, the threshold was raised to 70 and 97 mmHg, resulting in

also insufficient performances.[9,10] Palpation of arterial pulsations forms another cornerstone of clinical practice. However, it is not sufficient to diagnose or exclude PAD.[8,11-13]

So, it remains a clinical challenge to rule in and rule out PAD in patients prone to MAC, and we counsel against the use of a single bedside test. It is crucial to have a test that can reliably rule out PAD (i.e., have a low NLR). Because then PAD is less likely to be missed and more patients will be referred for additional imaging, CVRM and if necessary timely revascularization. Overall, the performance of the different bedside tests was generally disappointing and highly variable between studies of chapter 2. In addition, these studies often contained flaws in methodological quality. Risks of bias, concerns about applicability and small sample sizes were serious concerns regarding the reliability of the conventional bedside test. We advocate therefore for more methodologically well-designed studies to investigate the conventional bedside test. The following aspects should be taken into account when a new study is created: risk of bias and applicability concerns regarding selection of patients, index test (e.g., blinded to reference standard, threshold pre-specified) and reference standard (e.g., blinded to index test, correctly classify disease). In addition, care must be taken that all patients receive the same reference standard and all patients are included in analysis. Furthermore, next to new studies about conventional bedside tests, also new bedside tests must be investigated to improve the performance of non-invasive diagnostics.

To elaborate on this, a new DUS parameter, maximal systolic acceleration (ACCmax), was investigated. The ACCmax can be used for detecting arterial stenosis. In chapter 3 the basic principles of a new test were studied; the performance of the ACCmax in an experimental in vitro setting. The ACCmax decreased as the degree of the stenosis increased, with a good correlation regarding to changes in intraluminal pressure gradient ($R^2 = 0.937$). In chapter 4 an in vivo study is described, in which the ACCmax is compared to the conventional bedside tests. These chapters (3 and 4) comprise the fundament of the ACCmax validation in PAD, and showed that ACCmax is superior to ABI, TBI, TP, ACCsys and PSV in healthy study participants. However, prospective clinical studies are needed to determine the exact clinical value of ACCmax. As mentioned before, it is important to have a pre-specified index test threshold when creating a new prospective study. In chapter 4 we found in a hemodynamically significant stenosis (70% reduction in cross-sectional area) a mean ACCmax of 4.6 m/sec^2. This is in accordance with two previous published clinical studies which investigate the ACCmax to diagnose PAD. One study showed a high ACCmax (>10m/s^2) can exclude PAD with a negative predictive value of 95%. While an ACCmax of <6.5 m/s^2 is strongly indicative of the presence of PAD (positive predictive value of 99%).[14] Buschmann et al. determined an ACCmax threshold of 5.0 m/s^2 to diagnose PAD and showed a better area under the curve for ACCmax compared to ABI in patients with and without diabetes.[15]

Although the limiting number of studies investigating the ACCmax, the ACCmax appears to be more accurate in detecting PAD than the conventional bedside test.

At the moment, there is a need for a well-designed prospective study that will focus on the diagnostic value of ACCmax in patient with MAC. Particularly in this challenging group of patients, the ACCmax might benefit more compared to the conventional bedside test since no external pressure measurement is necessary, and ACCmax measurements can be obtained in a very short time (less than 1 minute). Furthermore, the methodology of measuring the ACCmax should be more standardize in order to improve the interobserver variability in a clinical setting.

Carotid artery stenosis

According to the international guidelines for carotid artery stenosis, DUS alone (without any other diagnostic tool) is an acceptable strategy to make a decision regarding intervention.[16,17] Therefore, reliable DUS measurements are crucial. All conventional DUS parameters (ICA PSV, PSV ratio (ICA/CCA), optical estimation of the stenosis, ICA EDV) are measured at the level of stenosis[18], making these parameters vulnerable for local distorting factors. Acoustic shadowing as a result of vascular calcification can hamper these conventional measurements, and may lead to inaccurate results.[19-22] To circumvent these local distorting factors ACCmax can be used. This alternative non-invasive parameter is measured distal to the stenosis in the distal extracranial ICA. In chapter 5 we presented the first results of the ACCmax in detecting an ICA stenosis. Using ACCmax an accurate distinction can be made concerning stenosis categories (<50%, 50-69%, ≥70%). To diagnose a ≥70% ICA stenosis a sensitivity of 90% and a specificity of 89% were found. And to diagnose a ≥50% ICA stenosis a sensitivity of 82% and a specificity of 88% were found. Although these good test performance for ACCmax, to diagnose a solitary ≥50% ICA stenosis the ICA PSV and PSV ratio were slightly superior compared to ACCmax. Note that the benefit of ACCmax is not in the accuracy of detecting an ICA stenosis, but in the ability to perform the measurement at an additional measuring point to avoid the influence of local distorting factors of a plaque.

Because chapter 5 describes the first insights of the ACCmax in ICA stenosis, we decided to investigate the value of ACCmax only at solitary ICA stenosis without prior ipsilateral intervention; in which the conventional DUS parameters has been proven. From here, future research can be initiated. In our opinion the following studies should focus on: I) evaluating ACCmax results in a prospective design to determine the performance of the cut-off values and interobserver agreement, II) potential benefits of ACCmax in specific subgroups such as patients with proximal stenosis (diagnosed by a decreased ACCmax in CCA) and extensive calcific shadowing of the ICA.

As mentioned in the introduction and shown in figure 3 of chapter 1 it is important to realize the differences between diameter and cross-sectional area reduction method. The landmark trials (NASCET and ECST)[23,24] determined thresholds based on diameter reduction. Although it is unclear if the degree of stenosis is different when using the area reduction method compared with the diameter reduction in a clinical setting, in individual patients it is clear that the degree of ICA stenosis can vary depending on which method is used.[25-28] In chapter 6 a questionnaire study shows that the quantification method on CTA to determine the degree of stenosis varies according to the type of plaque. The diameter reduction method is used most often for all plaque types, especially in regular/non-ulcerated and calcified plaques. However, the cross-sectional area reduction method is also used to determine the degree of stenosis, in particular for irregular/ulcerated plaques. In this type of plaque 45% either using the area reduction method exclusively or using both the diameter reduction and area reduction methods. Furthermore, 32% used the area reduction method as the sole method for an irregular/ulcerated plaque. This is remarkable because the current guideline does not consider measuring area reduction to be an option for determining the degree of stenosis.[16] Consequently, it may affect decision making for patient eligibility for carotid intervention. Therefore, we will argue for a uniform strategy to classify an ICA stenosis on CTA.

In our opinion, area reduction measurement should eventually be the preferred method to determine the degree of stenosis since evidence is found that this method is more accurate than the diameter reduction method, especially for irregular plaques.[25,27] Hence, first of all consensus must be reached if measurement of cross-sectional area reduction differs from measurement of diameter reduction in a clinical setting, before further elaboration of this topic.

Renal artery stenosis

Nowadays renal revascularization has a limited role since large clinical trials showed no benefit of revascularization compared to best medical treatment.[29-31] However, as a result of some criticism[32-34] about the design of these trials and multiple observational studies[35-37] suggesting beneficial outcome of renal revascularization, one can postulate that some patients will benefit from an intervention. In chapter 7 non-invasive parameters were identified that could have a predictive value for a positive response from revascularization. In previous studies, the intrarenal DUS parameter ACCmax emerged as an accurate non-invasive tool to diagnose RAS with a sensitivity of 83%–94%.[38-40] We made a prediction model (RI≤0.5 and ACCmax≤1.3 m/s^2) that enables selection of patients who have the potential to benefits from renal revascularization. As a result of the limited renal revascularization performed nowadays (leading to less inclusions), the expected statistical

characteristics of the prediction model must be interpreted with caution. Yet, this prediction model could lead to better selection of patients who have the potential to benefit from renal revascularization. Although this prediction model might be promising, it should be evaluated in a prospective study population to ensure its validity.

Conclusion

About a decade ago the ACCmax was hardly used for the analysis of atherosclerotic vascular disease, but fortunately the ACCmax has gained ground over the last years since more evidence has become available nowadays. As a result of the studies in this thesis, the foundation has been laid for the validation of ACCmax. It is of utmost importance that there is a continuous improvement in non-invasive diagnostics. The ACCmax might play an increasingly important role in atherosclerotic diseases over the next few years in patients with PAD (in particular with MAC) as well as patients with renal and carotid arterial disease.

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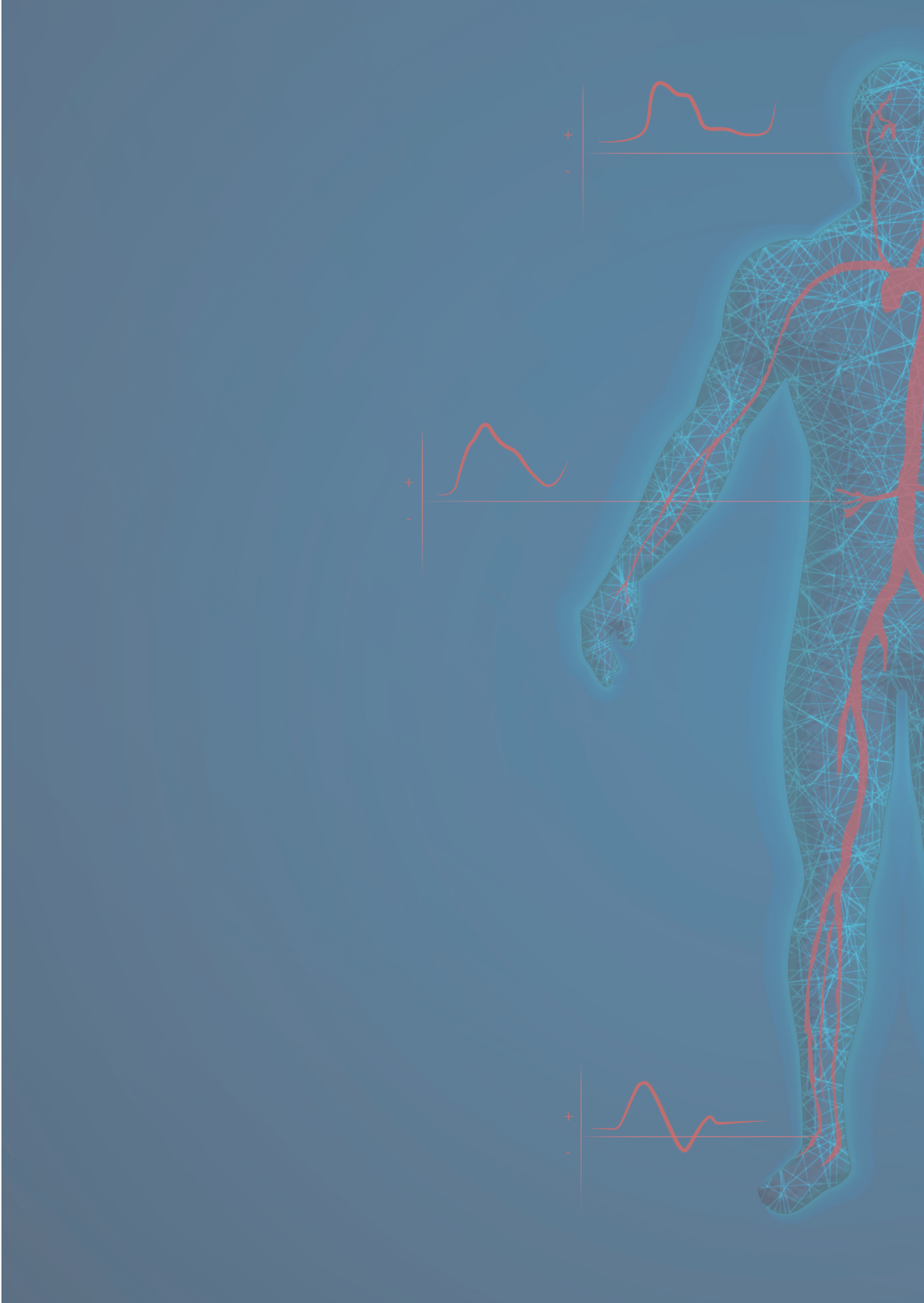
Chapter 9

Summary

Dutch summary
(Nederlandse samenvatting)



Summary

In this thesis we emphasize the importance of accurate non-invasive tools in atherosclerotic vascular diseases. Continuous improvement of these modalities is crucial in diagnostics and patient selection. Therefore, we investigate the new Doppler ultrasonography (DUS) parameter maximal systolic acceleration (ACCmax). Multiple clinical manifestations related to atherosclerosis can occur based on the location of the plaque. For example, cerebral ischemic attacks can occur as a result of a carotid artery stenosis, and an atherosclerotic stenosis in the lower extremity can lead to claudication intermittent. In accordance, in this thesis there is a distinction made in atherosclerotic vascular disease: peripheral arterial disease (PAD) of the lower extremity, carotid artery stenosis, and renal artery stenosis (RAS).

Part I Peripheral arterial disease of the lower extremity

PAD can primarily be assessed by the ankle brachial index (ABI), toe brachial index (TBI) and toe pressure (TP). However, in patients with diabetes mellitus (DM) or chronic kidney failure (CKD), medial arterial calcification (MAC) can occur leading to incompressible arteries and unreliable test results. Therefore, ABI, TBI and TP will not provide an adequate estimation of the blood flow to foot and toes in these patients. The prevalence of PAD in people with DM is 20-30%, and increases to 65% in patients with diabetic foot ulcer (DFU). MAC occurs in a third of the patients with DM, and is detected in 70% of the amputations for critical limb ischemia. It is expected that the number of patients with DM will increase to nearly 370 million people by 2030 worldwide. An accurate diagnosis of PAD in patients with MAC is important because timely recognition of critical limb ischemia is pertinent to reduce delayed wound healing, and prevent (major) lower limb amputation and mortality. Furthermore, early identification of PAD is essential to promptly start cardiovascular risk management (CVRM) and reduce the risk of cardiovascular events. Therefore, it is important to have reliable non-invasive bedside tests to diagnose PAD. We performed a systematic review (**Chapter 2**) to evaluate the reliability of non-invasive bedside tests compared to reference imaging techniques for diagnosing PAD in patients prone to MAC.

Remarkably, only 23 studies investigated the accuracy of bedside tests in patients prone to MAC. ABI is the most frequently used bedside test to diagnose PAD, and is accurate to diagnose PAD (PLR 8.72-17) when excluding patients with ABI >1.3. However, it is insufficient to exclude PAD (NLR 0.24-0.84). TBI or TP are often used in patients with MAC. However, these bedside tests are insufficient to diagnose or exclude PAD. Furthermore, regarding TP different thresholds were used to diagnose PAD (50, 70 and 97 mmHg) in

several studies. Also, the definition of an abnormal test was not consistent for continuous waveform Doppler (CWD) analysis. When a loss of a triphasic signal was used to determine PAD, PAD could be accurately ruled out (NLR 0-0.09). However, most patients with MAC have dampened, monophasic or biphasic waveforms, making a triphasic signal (to exclude PAD) less useful in clinical practice. Furthermore, the presence of palpable pedal pulses was insufficient to diagnose or exclude PAD.

So, in general the performance of the different bedside tests was insufficient and variable between studies. Therefore, we counsel against the use of a single bedside test. Furthermore, the methodological quality of the included studies was low (in 20 of the 23 studies a risk of bias or a concern regarding applicability was present) and sample sizes were small. More methodologically well designed studies are needed to evaluate the performance of the conventional bedside test in patients prone to MAC. Also, it is important to investigate new non-invasive diagnostic parameters to diagnose PAD in this challenging group of patients.

To address the need for new non-invasive tools, we investigated the DUS parameter maximal systolic acceleration (ACCmax). In particular for patients with MAC, the ACCmax might benefit more compared to the conventional bedside test since no external pressure measurement is necessary. It measures the acceleration of blood flow by quantifying the maximal slope of the systolic doppler curve, as shown in figure 1. The ACCmax is always measured distal to the stenosis, for example in distal posterior tibial artery. Moreover, ACCmax measurements can be obtained in a very short time (less than 1 minute).

In **chapter 3** fundamental research is shown in which ACCmax is investigated in an experimental in vitro setting. A circulatory flow system was used to imitate the human circulation. Furthermore, an arterial stenosis was made, which was built in the flow system, see also figure 1 in chapter 3. The following degrees of stenosis were used: 50%, 70%, 80%, and 90%. The ACCmax significantly decreased ($P < .001$), and the intraluminal mean arterial pressure gradient increased ($P < .001$) as the degree of stenosis increased. The correlation between ACCmax and the pressure gradient was strong ($R^2 = 0.937$). Also, a very low interobserver variability was determined with respect to ACCmax for 2 independent investigators (ICC = 0.99).

In **chapter 4** we develop the validation of ACCmax further; in an in vivo study setting the ACCmax was compared to the conventional bedside test. In twelve healthy individuals an arterial stenosis was mimicked by compression on the common femoral artery by an ultrasounds probe, creating a local stenosis of 50%, 70% and 90%. The ACCmax showed the highest correlation with the degree of stenosis (r -0.884), compared to ABI (r -0.726), TBI (r -0.716) and TP (r -0.758). Also, in this study the interobserver variability of ACCmax was very low (ICC 0.97).

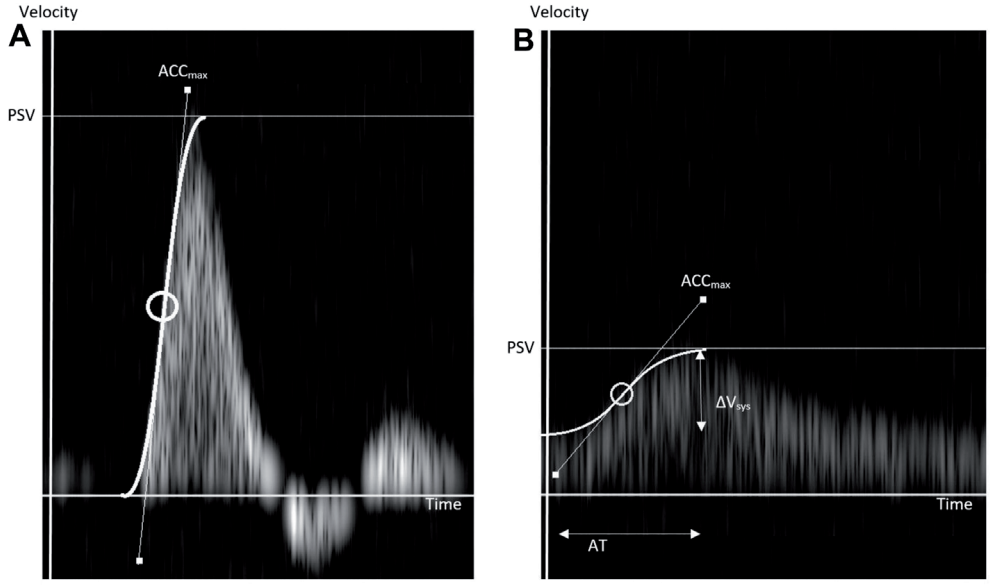


Figure 1: Example analysis of Doppler spectrum.
A, Normal triphasic Doppler waveform. Maximal systolic acceleration (ACCmax) is measured at inflection point at which upstroke changes from concave up to concave down. It is equal to slope of tangent line on curve at inflection point. B, Example of abnormal monophasic Doppler waveform. ACCmax, peak systolic velocity (PSV), acceleration time (AT), and systolic velocity gradient (ΔVsys) are shown. ACCmax is measured at visually judged maximum derivative of systolic phase.

Combining the results of chapter 3 and 4 ACCmax proved to be superior to ABI, TBI, TP, ACCsys and PSV in experimental settings. ACCmax can assess the severity of a stenotic disease, and has an excellent interobserver variability. Although these studies form the basis of the validation of the ACCmax, prospective clinical studies are needed to determine the exact clinical value of ACCmax. Particularly in patients with MAC the ACCmax might benefit more compared to the conventional bedside test since there is no external pressure measurement needed in obtaining the ACCmax.

Part II Carotid artery stenosis

In carotid artery disease non-invasive measurements are not only important to diagnose an internal carotid artery (ICA) stenosis, but also crucial for decision making regarding carotid intervention. The international guidelines mentioned the option of DUS alone (without any other diagnostic tool) as acceptable strategy to make a decision regarding intervention. Therefore, accurate DUS measurement is of the utmost importance. Conventional DUS parameter (ICA PSV, optical estimation of the stenosis, PSV ratio, ICA EDV) measurements are vulnerable for local distorting factors. Vascular calcification resulting in acoustic shadowing can hamper these four measurements, and may lead to inaccurate results. To circumvent these local distorting factors ACCmax can be used since it is measured distal to the stenosis (in the distal extracranial ICA).

A retrospective study was performed (**chapter 5**) to describe the first results of ACCmax in detecting ICA stenosis. The study population consisted of 947 different carotid arteries. By using the ACCmax a distinction can be made concerning stenosis categories since the ACCmax was significantly different between these stenosis categories (<50%, 50-69%, ≥70%). ACCmax decreased as the severity of stenosis increased. Furthermore, strong correlations between ACCmax and ICA PSV (R^2 0.88) and PSV ratio (R^2 0.87) were found, as shown in figure 3 of chapter 5.

To investigate which DUS parameter is the most accurate one, a subgroup analysis was performed. The ACCmax, ICA PSV and PSV ratio were compared to CTA as reference test. Based on the area under the curves (AUC) in ROC analysis, the optimal cut-off values were calculated, as shown in table 1. For diagnosing a ≥70% ICA stenosis there were no significant differences in AUC between these three parameters. However, to diagnose a solitary ≥50% ICA stenosis the ACCmax was somewhat inferior as compared to conventional Duplex parameters ICA PSV and PSV ratio. However, the benefit of ACCmax is not in the accuracy of detecting a simple mild ICA stenosis, but in the ability to perform the measurement at an additional measuring point to avoid the influence of local distorting factors of a plaque, as mentioned before. Therefore, ACCmax can be used as additional measurement, particularly when DUS is the only modality before decision making regarding intervention.

Our study presents the first ACCmax results in carotid artery disease. From here, future research can be initiated. In our opinion, the following studies should focus on: I) evaluating ACCmax results in a prospective design to determine the performance of the cut-off values and interobserver agreement, II) potential benefits of ACCmax in specific subgroups such as patients with proximal stenosis (diagnosed by a decreased ACCmax in CCA) and extensive calcific shadowing of the ICA.

	AUC (95% CI)	Optimal cut-off value	Sensitivity (%)	Specificity (%)	PLR	NLR
To diagnose ≥ 50% ICA stenosis						
ACCmax	0.88 (0.82-0.94)	7.15	82	88	6.83	0.20
ICA PSV	0.94 (0.91-0.97)	143	93	87	7.15	0.08
PSV ratio	0.94 (0.91-0.97)	1.77	88	89	8.00	0.13
To diagnose ≥ 70% ICA stenosis						
ACCmax	0.89 (0.82-0.95)	4.05	90	89	8.18	0.11
ICA PSV	0.94 (0.89-0.97)	212	86	90	8.60	0.16
PSV ratio	0.93 (0.89-0.97)	3.21	90	89	8.18	0.11

Table 1: Diagnostic performance characteristics of DUS parameters to identify ICA stenosis compared to CTA as reference test
Optimal cut-off values were calculated using Youden's index
AUC = area under the curve, PLR = Positive likelihood ratio, NLR = negative likelihood ratio, ACCmax = maximal systolic acceleration in m/sec^2, ICA PSV = internal carotid artery peak systolic velocity in cm/sec, PSV ratio = ICA PSV / CCA PSV

Although the international guidelines mention the option of DUS alone to make a decision regarding intervention, many centers obtained additional imaging (computed tomographic angiography (CTA) or MR angiography (MRA)) when intervention is considered. Large trials (NASCET and ECST) determined thresholds for intervention based on diameter reduction. The diameter reduction method has therefore been established as the standard quantification method to assess the degree of ICA stenosis. The diameter reduction method is nowadays being applied to CTA and MRA images. Alternatively, on CTA cross sectional area measurements can be performed; this method also considers the asymmetric shapes of a stenosis. For irregular plaques, cross-sectional area reduction might provide a more accurate quantification of ICA stenosis. However, the European guideline did not mention the option to use the cross-sectional area reduction method. In daily clinical practice, some radiologists measure the cross-sectional area reduction method to estimate the degree of stenosis, but it is unclear to what extent this occurs. The objective of **chapter 6** was therefore to determine which method is generally used. Hence, we generated a questionnaire study to investigate which method (reduction in diameter or area) radiologists typically use to assess the degree of ICA stenosis.

Ninety-two questionnaires were analyzed. The respondents consist of 83 neuroradiologists, 8 neuroradiology residents, and 1 neurosurgeon. Our survey showed that the method used to assess degree of ICA stenosis varies according to the type of plaque. For a regular/non-ulcerated and calcified plaque the diameter reduction was used most often to determine the degree of stenosis, respectively 67% and 62%. However, for an irregular/

ulcerated plaque the use of the area reduction method increased to 45% (use either the area reduction method exclusively or both the diameter reduction and area reduction methods). Interestingly, overall, a total of 42 respondents (46%) reported that they use the area reduction method—either exclusively or in addition to the diameter reduction method— for quantifying degree of carotid artery stenosis.

Although the area reduction method is suggested to be a more accurate method and theoretically might express the true hemodynamic significance of the lesion better than the diameter stenosis method, it is not validated for selecting patients regarding intervention. In our opinion, as long as there is no consensus if measurement of the area reduction differs from measurement of the diameter reduction in a clinical setting, caution must be taken when the area reduction method is used to select patients for intervention.

Part III Renal artery stenosis

Renal revascularization might improve renal function and blood pressure control in patients with renal artery stenosis (RAS). However, technically successful revascularization does not guarantee positive responses in terms of blood pressure regulation or preservation of renal function. The objective of **chapter 7** was to identify prognostic parameters that can select patients who will benefit from renal revascularization. We hypothesized that the resistive index (RI) and ACCmax might have this prognostic value.

For diagnosing RAS there are various strategies. The ACCmax can be used to detect a significant RAS with a sensitivity of 83–94%. The RI is a measure of pulsatile blood flow and is modified by vascular resistance and vascular compliance. A high RI suggests no improvement in renal function and blood pressure after renal revascularization. However, it is not clear which patients will have a positive response from revascularization. Both measurements (ACCmax and RI) are obtained from the interlobar artery (intrarenal), in contrast with the PSV or PSV ratio which are measured in the main renal artery. Thirty-two patients who underwent a renal revascularization procedure were included. To distinguish a positive response from a non-responder the renal function (eGFR) and mean arterial pressure (MAP) were used six months after intervention. In total 13 combined positive responders and 19 combined non-responders were founded in the study population.

The combined positive responders had a significant lower median RI and lower median ACCmax than the combined non-responders. Furthermore, a prediction model was calculated (RI≤0.5 and ACCmax≤1.3 m/s^2). The prediction model classifies patients as expected positive responders if the patient scored at or below the respective cut-off points on both variables. The performance of this prediction model is shown in table 2;

an expected sensitivity of 69% and specificity of 89% for a positive response after renal revascularization was calculated. In conclusion, our prediction model is a new objective non-invasive instrument which has a contributing role in decision making regarding treatment of RAS. Although this prediction model might be promising, it should be evaluated in clinical prospective studies to ensure its validity.

Sensitivity	69%
Specificity	89%
Positive predictive value	82%
Negative predictive value	81%

Table 2: Expected statistical characteristics of the prediction model (based on double-cross-validation computation)

Dutch summary (Nederlandse samenvatting)

In dit manuscript wordt de accuraatheid van non-invasief onderzoek geëvalueerd bij patiënten met atherosclerotische aandoeningen. Continue verbetering van deze modaliteiten is cruciaal voor de diagnostiek en patiënten selectie voor bijvoorbeeld een behandeling. Daarom hebben we de nieuwe echo Doppler (DUS) parameter maximale systolische acceleratie (ACCmax) onderzocht. Verschillende klinische manifestaties kunnen optreden door atherosclerose. Voorbeelden zijn een herseninfarct als gevolg van een carotisstenose en een atherosclerotische stenose in de onderste extremiteit kan leiden tot claudicatio intermittens. In dit manuscript is daarom onderscheid gemaakt tussen verschillende atherosclerotische ziektebeelden: perifeer arterieel vaatlijden (PAV) van de onderste extremiteit, carotisstenose en nierarteriestenose.

Deel I Perifeer arterieel vaatlijden (PAV) van de onderste extremiteit

De aanwezigheid van PAV kan primair worden beoordeeld door de enkel-arm index (EAI), teen-arm index (TAI) en de absolute teendruk (TD). Echter, bij patiënten met diabetes mellitus (DM) of chronische nierfalen kan arteriële mediasclerose (MAC) optreden wat leidt tot niet-comprimeerbare vaten en onbetrouwbare testuitslagen. Vandaar dat de EAI, TAI en TD geen geschikte testen zijn in deze patiëntencategorieën om de bloedflow naar de voeten en tenen te beoordelen. De prevalentie van PAV bij patiënten met DM is 20-30% en stijgt naar 65% bij patiënten met een diabetische voet (DFU). MAC komt voor bij een derde van de patiënten met DM en wordt bij 70% van de patiënten gedetecteerd die een amputatie hebben ondergaan vanwege kritieke ischemie. Naar verwachting zal de patiëntenpopulatie met DM alleen maar stijgen; in 2030 zullen er waarschijnlijk 370 miljoen patiënten zijn met DM. Het accuraat stellen van de diagnose PAV bij patiënten met MAC is belangrijk aangezien tijdige herkenning van kritieke ischemie relevant is om vertraagde wondgenezing te reduceren, en (majeure) amputatie en mortaliteit te voorkomen. Daarnaast is vroegtijdige herkenning van PAV essentieel om direct te starten met het cardiovasculair risico management (CVRM) en daarmee reductie van cardiovasculaire events te bewerkstellingen. Daarom zijn betrouwbare non-invasieve bedside testen erg belangrijk om de diagnose PAV te stellen. Wij hebben een systematische review (**hoofdstuk 2**) uitgevoerd om de betrouwbaarheid van deze non-invasie bedside testen naar PAV te

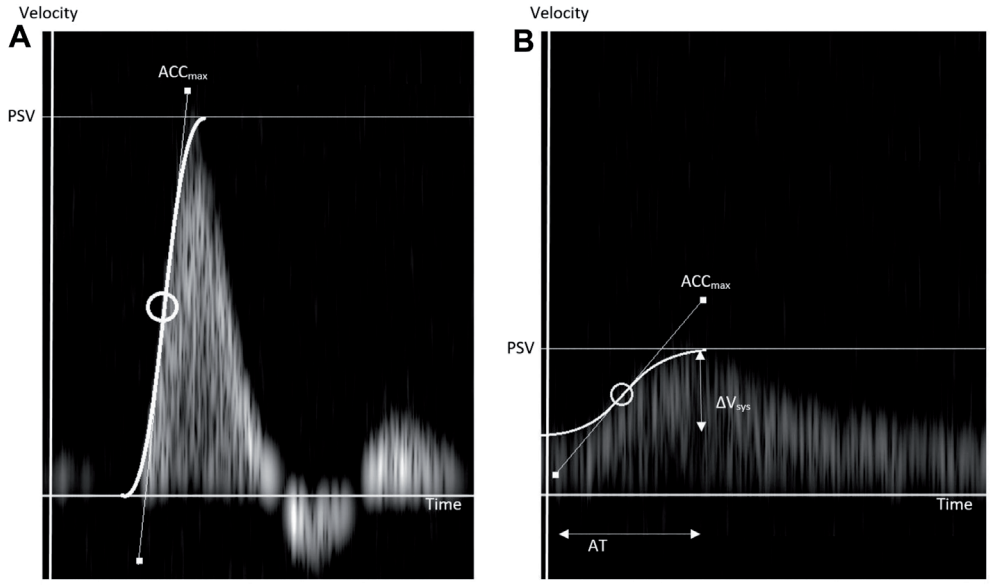
evalueren bij patiënten die prone zijn voor MAC. Hierbij is van belang dat de non-invasie bedside testen zijn vergeleken met betrouwbare referentie testen.

Het is opvallend dat maar 23 studies onderzoek hebben gedaan naar de betrouwbaarheid van bedside testen om PAV aan te tonen in patiënten prone voor MAC. De EAI is de meest gebruikte bedside test en is accuraat om PAV aan te tonen (PLR 8.72-17) op het moment dat patiënten met een EAI >1.3 zijn geëxcludeerd. De EAI is echter insufficiënt om PAV te excluderen (NLR 0.24-0.84). De TAI en TD worden vaak gebruikt bij patiënten met MAC. Maar deze bedside testen zijn insufficiënt om PAV aan te tonen en uit te sluiten. Bovendien worden er in de verschillende studies verschillende afkapwaardes van de TD gebruikt om PAV te diagnosticeren (50, 70 en 97 mmHg). Ook de definitie van een abnormale Dopper golfvorm (CWD) is niet consistent. Wanneer het verlies van een trifasisch signaal diagnostisch is voor PAV, kan PAV nauwkeurig worden uitgesloten middels CWD (NLR 0-0.09). Maar de meest patiënten met MAC hebben een gedempt, monofasisch of bifasisch signaal, waardoor een trifasisch signaal (om PAV te excluderen) minder bruikbaar is in de kliniek. Daarnaast is de aanwezigheid van palpabele pedale pulsaties insufficiënt om PAV te excluderen.

De nauwkeurigheid van de verschillende bedside testen is dus over het algemeen insufficiënt en variabel tussen de verschillende studies. Daarom pleiten wij tegen het gebruik van een enkele bedside test om PAV te diagnosticeren bij patiënten met MAC. Daarnaast is het opmerkelijk dat de methodologische kwaliteit van de geïncludeerde studies matig was (in 20 van de 23 studies is er risico op bias of zijn er zorgen over de toepasbaarheid) en waren de studiepopulaties klein. Er zijn meer methodologisch goede studies nodig om de eigenschappen van de conventionele bedside testen te onderzoeken bij patiënten die prone zijn voor MAC. Daarnaast is het ook belangrijk dat er nieuwe non-invasieve diagnostische parameters worden onderzocht in deze uitdagende patiëntenpopulatie.

Om deze vraag naar nieuwe non-invasieve diagnostische parameter te adresseren, hebben we onderzoek gedaan naar de DUS parameter maximale systolische acceleratie (ACCmax). Met name bij patiënten met MAC zou de ACCmax voordelen hebben ten opzichte van de conventionele bedside testen aangezien er geen externe drukmeting hoeft te worden verricht. Bij de ACCmax wordt de acceleratie van de bloedflow gemeten van de maximale helling in de systolische fase, zoals te zien is in figuur 1. De ACCmax wordt altijd distaal van de stenose gemeten, bijvoorbeeld in de arteria tibialis posterior (ATP). Bovendien kan de ACCmax in een korte tijd (minder dan 1 minuut) worden gemeten.

In **hoofdstuk 3** wordt fundamenteel onderzoek beschreven waarin de ACCmax in een experimentele in vitro setting is onderzocht. Bij dit onderzoek was een flow model gebruikt om een menselijke circulatie na te bootsen. Daarnaast was er een stenose model gemaakt



Figuur 1: voorbeelden van Doppler spectrum analyse
A, normale trifasische Doppler golfvorm. De maximale systolische acceleratie (ACCmax) wordt gemeten ter plaatse van de maximale helling. B, een voorbeeld van een abnormale monofasisch Doppler golfvorm. De ACCmax, piek systolische snelheid (PSV), acceleratie tijd (AT), systolische snelheidsgradiënt (ΔVsys) zijn weergegeven in het figuur. De ACCmax wordt visueel bepaald op de maximale helling in de systolische fase.

die in het flow model is geïmplementeerd, zoals te zien is in figuur 1 van hoofdstuk 3. De volgende stenose gradaties zijn gebruikt: 50%, 70%, 80%, en 90%. De ACCmax daalde significant ($P < .001$) en de intraluminale arteriële drukgradiënt steeg ($P < .001$) als de stenose gradatie steeg. De correlatie tussen de ACCmax en intraluminale arteriële drukgradiënt was sterk ($R^2 = 0.937$). Verder was er een erg lage interobserver variabiliteit voor de ACCmax tussen twee onafhankelijke onderzoeken (ICC = 0.99).

In **hoofdstuk 4** gaan we verder met de validatie van de ACCmax. In een in vivo setting werd de ACCmax vergeleken met de conventionele bedside testen. Bij twaalf gezonde proefpersonen werd een stenose nagebootst door middel van compressie van een echo transducer op de arterie femoralis communis (AFC), waardoor een stenose van 50%, 70% en 90% werd gecreëerd. De ACCmax liet de hoogste correlatie zien met de stenose graad (r -0.884), vergeleken met de EAI (r -0.726), TAI (r -0.716) en TD (r -0.758). Ook in deze studie was de interobserver variatie van de ACCmax erg laag (ICC 0.97).

Als we de resultaten van hoofdstuk 3 en 4 combineren is de ACCmax superieur ten opzichte van de EAI, TAI, TD, ACCsys en PSV in een experimentele setting. De ACCmax kan de ernst

van het vaatlijden weergeven en heeft een goede interobserver variabiliteit. Ondanks dat deze studies de basis van de validatie van de ACCmax vertegenwoordigen, zijn prospectieve klinische studies nodig om de exacte klinische waarde van de ACCmax te bepalen. Met name bij patiënten met MAC lijkt de ACCmax een voordeel te hebben ten opzichte van de conventionele bedside testen aangezien er geen externe druk wordt gegenereerd bij het meten van de ACCmax.

Deel II Carotisstenose

Bij een carotisstenose zijn de non-invasieve metingen niet alleen belangrijk bij het stellen van de diagnose van een arteria carotis interna (ICA) stenose, maar ook cruciaal voor het maken van het beleid zoals een carotis interventie. De internationale richtlijnen geven de optie om met alleen DUS (zonder een andere diagnostische modaliteit) een beleid te maken met betrekking tot een interventie. Daarom is een accurate DUS meting van cruciaal belang. De conventionele DUS metingen (ICA PSV, optische schatting stenosegraad, PSV ratio, ICA EDV) kunnen worden gecomprimeerd door lokale verstorende factoren. Een gecalcificeerde plaque resulteert in akoestische schaduw op de DUS waardoor de conventionele metingen kunnen worden verstoord, wat kan leiden tot inaccurate resultaten. Om deze lokale verstorende factoren te omzeilen kan de ACCmax worden gebruikt, aangezien deze meting distaal van de stenose wordt bepaald (in het distale extracraniële gedeelte van de ICA).

Een retrospectieve studie is uitgevoerd (**hoofdstuk 5**) om de eerste resultaten van de ACCmax te onderzoeken voor het detecteren van een ICA stenose. De studiepopulatie bestond uit 947 verschillende carotiden. Aangezien de ACCmax significant verschillend was tussen verschillende stenosegradatie groepen (<50%, 50-69%, ≥70%), kan er middels de ACCmax onderscheid worden gemaakt tussen deze verschillende stenosegradaties. De ACCmax daalt op het moment dat de ernst van de stenosegraad stijgt. Daarnaast was er een sterke correlatie tussen de ACCmax en de ICA PSV (R^2 0.88) en PSV ratio (R^2 0.87), zoals ook te zien is in figuur 3 van hoofdstuk 5.

Om te beoordelen welke DUS parameter het meest accuraat is, werd een subgroep analyse uitgevoerd. De ACCmax, ICA PSV en PSV ratio werden vergeleken met de CTA als referentie test. De optimale afkapwaardes werden bepaald door middel van *area under the curves* (AUC) met ROC analyses, zoals te zien is in tabel 1. Voor het diagnosticeren van een ≥70% ICA stenose werden geen significante verschillen gevonden in AUC tussen deze drie parameters. Voor het diagnosticeren van een ≥50% ICA stenose was de ACCmax iets inferieur ten opzichte van de conventionele DUS parameter ICA PSV en PSV ratio. Het voordeel van de ACCmax is niet de accuraatheid van het diagnosticeren van een simpele milde ICA stenose, maar de mogelijkheid om het op een ander meetpunt te bepalen

	AUC (95% CI)	Optimale afkapwaarde	Sensitiviteit (%)	Specificiteit (%)	PLR	NLR
Diagnosticeren ≥ 50% ICA stenose						
ACCmax	0.88 (0.82-0.94)	7.15	82	88	6.83	0.20
ICA PSV	0.94 (0.91-0.97)	143	93	87	7.15	0.08
PSV ratio	0.94 (0.91-0.97)	1.77	88	89	8.00	0.13
Diagnosticeren ≥ 70% ICA stenose						
ACCmax	0.89 (0.82-0.95)	4.05	90	89	8.18	0.11
ICA PSV	0.94 (0.89-0.97)	212	86	90	8.60	0.16
PSV ratio	0.93 (0.89-0.97)	3.21	90	89	8.18	0.11

Tabel 1: diagnostische eigenschappen van DUS parameters om een ICA stenose te detecteren met een CTA als referentie test
Optimale afkapwaardes zijn berekend middels de Youden's index
AUC = area under the curve, PLR = positieve likelihood ratio, NLR = negatieve likelihood ratio, ACCmax = maximale systolische acceleratie in m/sec^2, ICA PSV = arteria carotis interna pieksystolische snelheid in cm/sec, PSV ratio = ICA PSV / CCA PSV

waardoor lokale verstorende factoren worden vermeden, zoals eerder uitgelegd. Daarom kan de ACCmax goed worden gebruikt als additionele DUS meting, met name in centra waar DUS de enige modaliteit is voor het bepalen van een behandeling.

Onze studie presenteert de eerste resultaten over de ACCmax bij een carotisstenose. Vanuit deze resultaten kan meer onderzoek worden geïnitieerd. De volgende studies zouden zich kunnen focussen op: I) de ACCmax evalueren in een prospectief design om de statistische eigenschappen van de afkapwaardes en de interobserver variabiliteit te bepalen; II) potentiële voordelen van de ACCmax in specifieke subgroepen, zoals bij patiënten met een proximale stenose (te diagnosticeren middels een verlaagde ACCmax in de CCA) of een heftig gecalcificeerde ICA stenose.

Ondanks dat internationale richtlijnen de optie geven om met alleen de DUS een beleid te maken met betrekking tot een interventie, wordt er in de meeste centra additionele beeldvorming verricht (computertomografische angiografie (CTA) of MR angiografie (MRA)). Grote studies (NASCET en ECST) hebben de afkapwaardes bepaald wanneer iemand in aanmerking komt voor een interventie; deze afkapwaardes zijn gebaseerd op diameter reductie. Vandaar dat de diameter reductie de standaard methode is om een stenosegraad te kwantificeren. De diameter reductie methode is doorgevoerd in de CTA en MRA. Een alternatief is de area reductie methode die bijvoorbeeld met de CTA kan worden bepaald. In deze methode wordt ook de asymmetrie van een stenose meegenomen. Voor irregulaire plaques kan de area reductie methode een meer nauwkeurige kwantificatie zijn. De

Europese richtlijn geeft echter niet de optie om de area reductie methode te gebruiken. Daarentegen zijn er radiologen die de area reductie methode al wel gebruiken in de dagelijkse praktijk om de stenosegraad te bepalen; het is nog onbekend in welke mate deze meetmethode wordt gebruikt. Vandaar dat er in **hoofdstuk 6** is onderzocht welke meetmethode er wordt gebruikt in de dagelijkse praktijk. We hebben voor deze studie een vragenlijst ontwikkeld om te onderzoeken welke meetmethode (diameter of area reductie) normaal gesproken wordt gebruikt door een radioloog om de stenosegraad van een ICA stenose te bepalen.

Tweeënnegentig vragenlijsten zijn geanalyseerd. De respondenten bestaan uit 83 neuroradiologen, 8 neuroradiologen in opleiding en 1 neurochirurg. Ons onderzoek laat zien dat de meetmethode die gebruikt wordt, varieert en afhangt van het type plaque. De diameter reductie wordt voor een regulaire/niet ulceratieve plaque en een gecalcificeerde plaque het meest gebruikt, namelijk in respectievelijk 67% en 62% van de gevallen. Echter, voor een irregulaire/ulceratieve plaque stijgt het percentage dat de area reductie methode wordt gebruikt naar 45% (alleen de area reductie werd gebruikt of de area reductie in combinatie met de diameter reductie methode). Het is opvallend dat 42 respondenten (46%) hebben gerapporteerd dat ze de area reductie methode gebruiken – exclusief of in combinatie met de diameter reductie methode – om de stenosegraad van een carotisstenose te bepalen.

Ondanks dat de area reductie methode mogelijk accurater is en theoretisch een betere expressie geeft van de hemodynamische impact van de stenose, is de area reductie methode (nog) niet gevalideerd om patiënten te selecteren voor een interventie. Vandaar dat wij van mening zijn dat, zolang er geen consensus is of de meetuitslagen van de area reductie methode significant anders zijn in een klinische setting dan die van de diameter reductie methode, men erg zorgvuldig moet zijn met het gebruik van de area reductie methode bij de selectie van patiënten voor een interventie.

Deel III Nierarteriestenose

Renale revascularisatie kan verbetering geven in de nierfunctie en bloeddrukregulatie bij patiënten met een nierarteriestenose (NAS). Maar een technisch succesvolle revascularisatie geeft niet de garantie dat er ook een positieve respons is in de bloeddrukregulatie of het behoud van nierfunctie. De doelstelling van **hoofdstuk 7** was om prognostische parameters te identificeren waardoor er patiënten kunnen worden geselecteerd die mogelijk voordeel hebben van een renale revascularisatie. Onze hypothese was dat de resistive index (RI) en ACCmax een prognostische waarde hebben.

Om NAS te diagnosticeren zijn verschillende strategieën mogelijk. De ACCmax kan een significante NAS detecteren met een sensitiviteit tussen de 83-94%. De RI is een meting van de pulsatiele bloedflow en is afhankelijk van de vasculaire weerstand en vasculaire compliantie. Een hoge RI suggereert dat er geen verbetering optreedt in nierfunctie of bloeddrukregulatie na een renale revascularisatie. Het is echter niet duidelijk welke patiënten wel een positieve respons hebben na een revascularisatie. Beide metingen (ACCmax en RI) worden verkregen in de arteria interlobularis (intra-renaal), in tegenstelling tot de PSV of PSV ratio die in de nierarterie worden verkregen.

Tweeëndertig patiënten die een renale revascularisatie hebben ondergaan, werden geïncludeerd in deze studie. Om onderscheid te maken tussen een positieve responder en een non responder werden de nierfunctie (eGFR) en mean arterial pressure (MAP) 6 maanden na een interventie gebruikt. In totaal waren er 13 *gecombineerde positieve responders* en 19 *gecombineerde non responders* in de studiepopulatie. De *gecombineerde positieve responders* hadden een significant lagere mediane RI en lagere mediane ACCmax dan de *gecombineerde non responders*. Daarnaast was er een predictie model opgesteld (RI≤0.5 en ACCmax≤1.3 m/sec^2). Dit predictie model classificeert een patiënt als een verwachte positieve responder indien de patiënt een lagere RI en lagere ACCmax heeft dan de eerdergenoemde afkapwaardes. De statistische eigenschappen van dit predictiemodel zijn weergegeven in tabel 2; een verwachte sensitiviteit van 69% en specificiteit van 89% voor een positieve response na een renale revascularisatie. Concluderend is ons predictiemodel een nieuw objectief instrument dat kan bijdragen aan de besluitvoering van de behandeling van NAS. Ondanks dat dit predictiemodel veelbelovend is, moet dit model eerst worden geëvalueerd in een klinische prospectieve studie om de validiteit te waarborgen.

Sensitiviteit	69%
Specificiteit	89%
Positief voorspellende waarde	82%
Negatief voorspellende waarde	81%

Tabel 2: Verwachte statistische eigenschappen van het predictiemodel (gebaseerd op dubbele kruisvalidatie berekeningen)

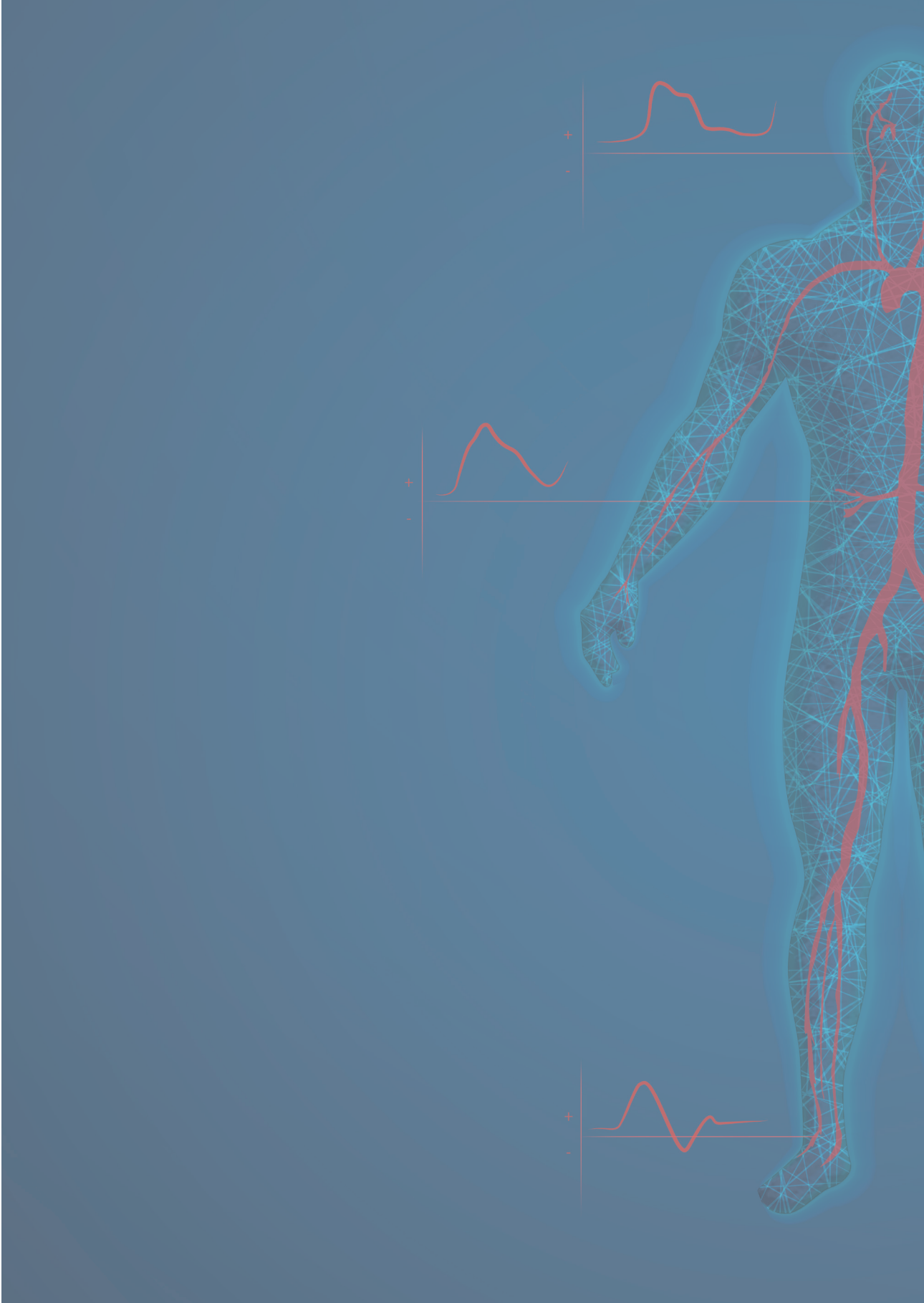
Appendices

List of publications

Curriculum Vitae

Dankwoord

Abbreviations



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Curriculum vitae

Jeroen Brouwers werd geboren op 25 november 1988 te Eindhoven. Hij behaalde zijn VWO-diploma aan het Stedelijk College te Eindhoven in 2007. Datzelfde jaar startte hij zijn studie Geneeskunde aan het Leids Universitair Medisch Centrum (LUMC). Tijdens zijn studie begon hij met wetenschappelijk onderzoek en raakte hij geïnteresseerd in de Vaatchirurgie. Ook doceerde hij anatomie in de snijzaal aan jongere mede Geneeskunde studenten. Zijn interesse voor de Chirurgie werd versterkt tijdens zijn co-schap Heelkunde en semi-artsstage bij de Vaatchirurgie in het LUMC. Daar kwam de wetenschap en kliniek bijeen. Nadat hij zijn studie succesvol had afgerond, was hij in 2014 zijn loopbaan begonnen als ANIOS in het Groene Hart Ziekenhuis te Gouda. Hier ervoer hij hoe het kan zijn om als beginnende assistent een dienstpieper op zak te hebben… Vervolgens maakte hij in 2016 de overstap naar het LUMC om daar zijn exposure aan chirurgische pathologie te vergroten. In 2017 was hij klaar om mee te solliciteren voor de opleiding tot Chirurg. Dit werd ook zo bevonden door de regionale opleidingscommissie waarna hij in juli 2017 met zijn opleiding tot chirurg kon starten. Hij startte zijn opleiding in het LUMC waar hij met veel plezier zijn eerste chirurgische vaardigheden ontwikkelde. In het tweede jaar van zijn opleiding maakte hij de overstap naar het HagaZiekenhuis te Den Haag. Gedurende deze periode groeide zijn interesse in de Vaatchirurgie steeds verder, waardoor hij in juli 2021 met veel plezier besloot te kiezen voor de differentiatie Vaatchirurgie.

Gedurende zijn opleiding tot chirurg heeft Jeroen ook zijn passie voor de wetenschap niet verloren. Hij zag het als een extra uitdaging om naast zijn opleiding ook wetenschappelijke activiteiten te blijven ondernemen, met als doel te promoveren voordat hij een jonge klare is. Met enthousiasme en commitment is het gelukt om dit proefschrift tijdig te voltooien. Het wetenschappelijke fundament van de maximale systolische acceleratie (ACCmax) is hiermee gelegd, maar dat wil niet zeggen dat hiermee zijn wetenschappelijke pad eindigt. Jeroen zal zich de komende jaren verder inzetten om de ACCmax te valideren en is reeds betrokken bij meerdere multicenter projecten.

Dankwoord

Dit proefschrift heb ik alleen kunnen schrijven met hulp van anderen. Middels de volgende woorden wil ik jullie bedanken.

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Vanaf mijn semi-arts periode kwam ik al onaangekondigd bij jou binnen, **Rob van Wissen**. Je maakte elke keer tijd voor mij, ook al had je een drukke wachtkamer. Dit gebeurt overigens tot op de dag van vandaag nog steeds. Bedankt daarvoor!

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Ook de vakgroep **Heelkunde** van het **HagaZiekenhuis**, in het bijzonder het **Vaatchirurgisch team** en de opleiders (**Jan Wever** en **Alexander Greeven**), wil ik bedanken voor de steun en interesse. Van jullie heb ik de ruimte gekregen om aan mijn wetenschappelijke projecten te werken. Ook wil ik alle **arts-assistenten** bedanken waar ik de afgelopen jaren mee heb mogen werken.

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Dan mijn paranimfen **Sebas** en **Arjen. Sebas**, huisgenoot, club-genoot, dispuut-genoot en bovenal vriend. Man, wat hebben wij veel meegemaakt, 'n tijd die ik nooit had willen missen. Ik kan altijd op je rekenen, dat waardeer ik heel erg!

Arjen, een huisarts met een chirurgische blik. Ook ik kan me de dag nog goed herinneren dat we over het Rap liepen, beiden vol enthousiasme haha. En kijk nou waar we nu staan. Dat hebben we toch maar mooi voor elkaar gekregen, vriend!

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Abbreviations

ABI	ankle-brachial Index
ACCmax	maximal systolic acceleration
ACCsys	mean systolic acceleration
AIE	external iliac artery
AP	ankle pressure
AT	acceleration time
AUC	area under the curve
CCA	common carotid artery
CEA	carotid endarterectomy
CIA	common iliac artery
CKD	chronic kidney disease
CLI	critical limb ischemia
CLTI	chronic limb threatening ischemia
CTA	computed tomographic angiography
CVRM	cardiovascular risk management
CWD	continuous wave Doppler analysis
DFU	diabetic foot ulcer
DM	diabetes mellitus
DSA	digital subtraction angiography
DUS	Doppler ultrasonography
ECST	European Carotid Surgery Trial
EDV	end-diastolic velocity
eGFR	estimated glomerular filtration rate
FMD	fibromuscular dysplasia
ICA	internal carotid artery
ICC	intraclass correlation coefficient
MAC	medial arterial calcification
MAP	mean arterial pressure
MDRD	modification of diet in renal disease
MRA	magnetic resonance angiography
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NLR	negative likelihood ratio
NPV	negative predictive value
NTx	renal transplant recipients
PAD	peripheral arterial disease
PI	pulsatility index

PLR	positive likelihood ratio
PPG	photoplethysmography
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSV	peak systolic velocity
PSV ratio	PSV ICA/PSV CCA
PTRA	percutaneous transluminal angioplasty interventions without a stent
PTRAS	percutaneous transluminal angioplasty interventions with a stent
RAS	renal artery stenosis
RI	resistive index
RPSI	relative pulse slope index
SD	standard deviation
TBI	toe-brachial index
TcPO2	Transcutaneous oxygen pressure
TIA	transient ischemic attack
TP	toe pressure
ΔVsys	systolic velocity gradient