Maximal systolic acceleration in atherosclerotic vascular disease

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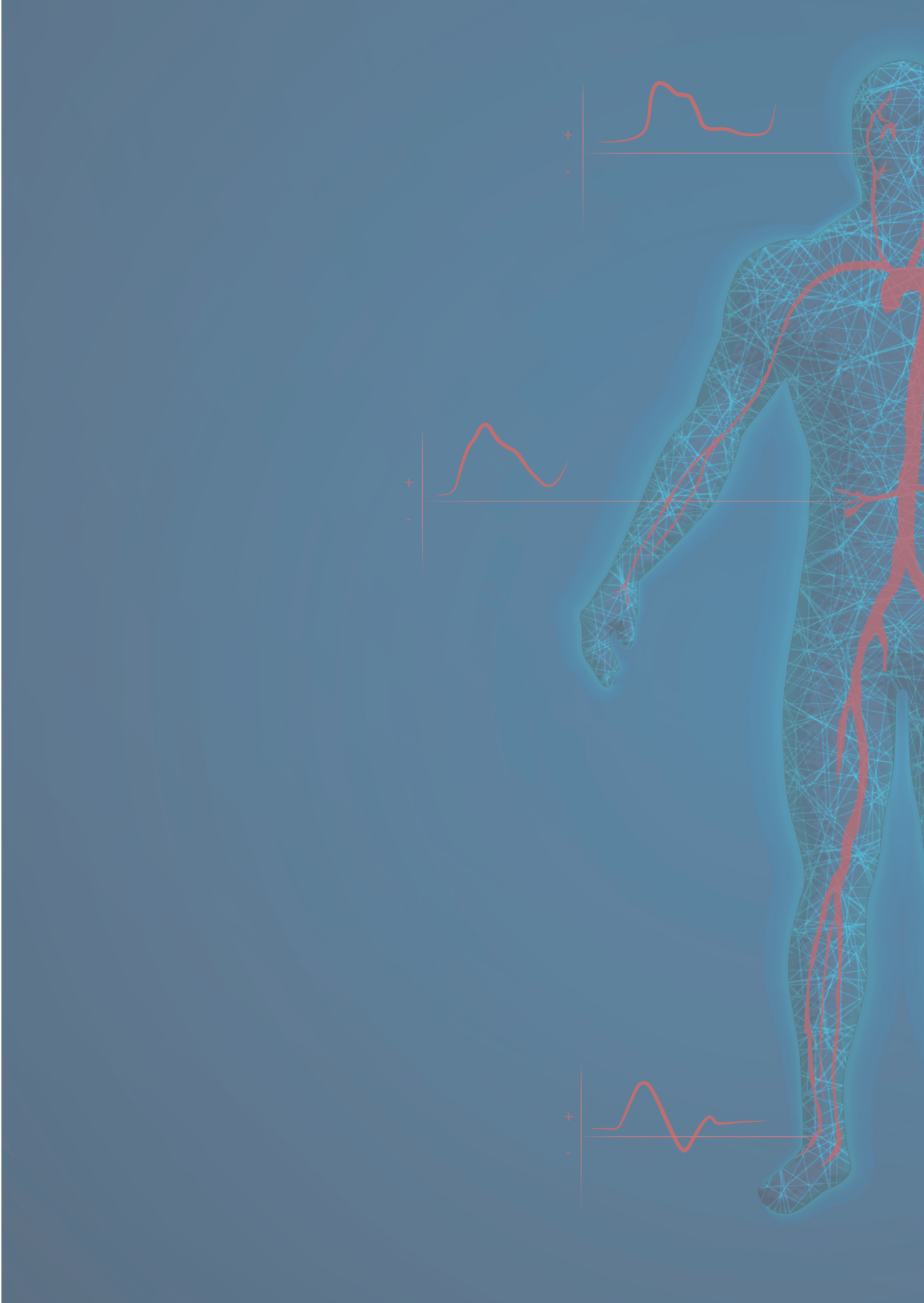
Chapter 1

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]

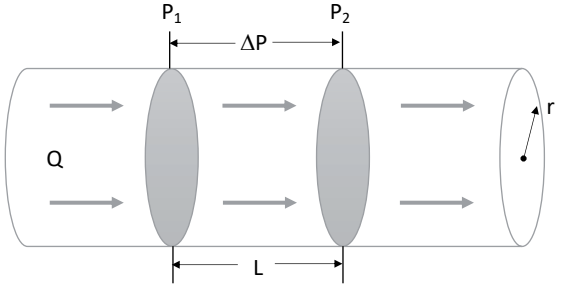
Although atherosclerosis is a generalized disease, it has several preferred locations to develop: carotid bifurcation, aortic arch branches, coronary arteries, aortic bifurcation, iliac vessels, femoral bifurcation, superficial femoral artery and lower leg vessels. Due to the different locations of an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

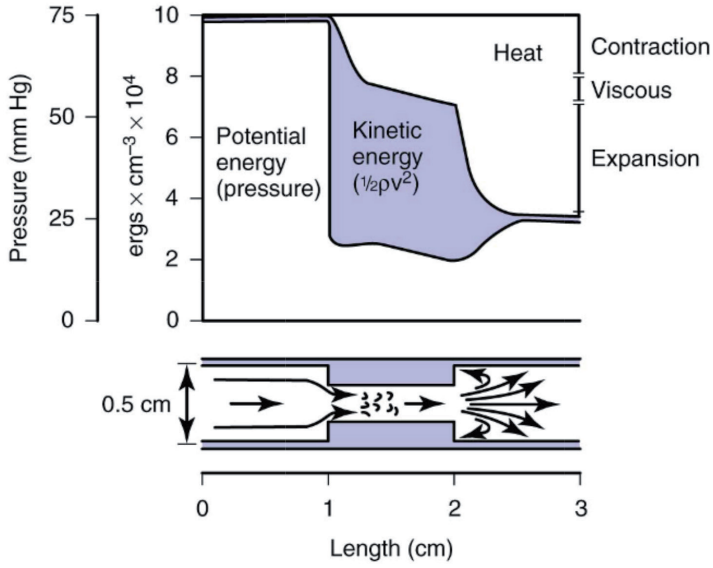


Figure 2: energy losses through a stenosis
In this figure the energy losses by blood are shown for a 1 cm long stenosis. Flow is assumed to be unidirectional and steady
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In **chapter 3** these arterial hemodynamic principles are implemented in a modified 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.

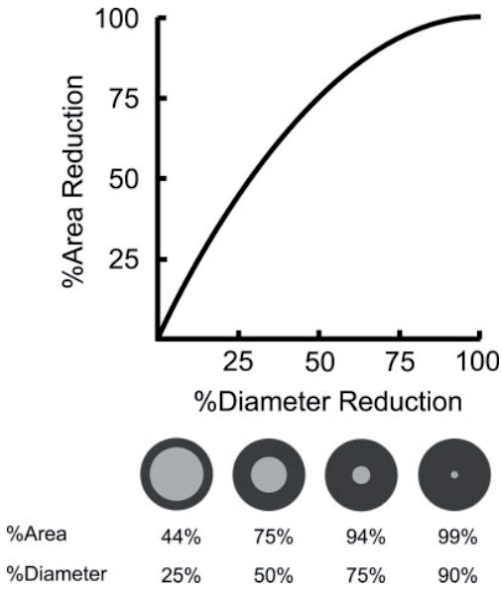

Figure 3: Relation between diameter and cross-sectional area reduction
The relationship is shown between diameter and cross-sectional area reduction in a completely concentric stenosis. The following equation is used A = D X (2-(D/100)
A = percentage of area reduction
D = percentage of diameter reduction.
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

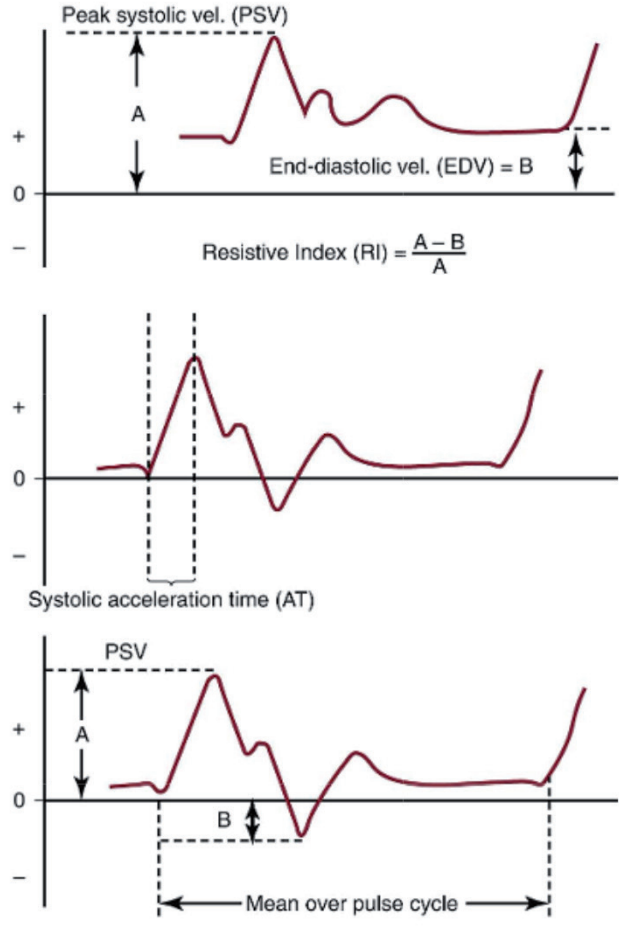

Figure 4: Doppler spectrum
Several Doppler spectral parameters are shown.
PSV = peak systolic velocity, EDV = end-diastolic velocity, RI = resistive index, and AT acceleration time.
This figure was published in Rutherford's Vascular Surgery 2014, Cronenwett et al. chapter: A Vascular Laboratory, page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

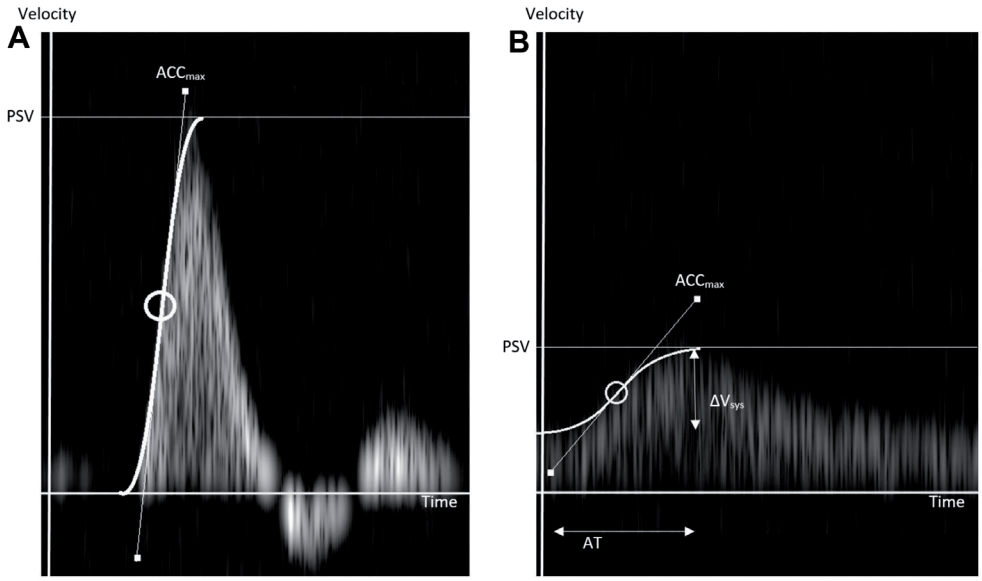

Figure 5: Example analysis of Doppler spectrum.
A, Normal triphasic Doppler waveform. Maximal systolic acceleration (ACCmax) is measured at inflection point at which upstroke changes from concave up to concave down. It is equal to slope of tangent line on curve at inflection point. B, Example of abnormal 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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