Carotid imaging in cardiovascular risk assessment

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CHAPTER 1

Introduction

CAROTID ARTERY IMAGING

Applications in cardiovascular risk assessment and pathophysiological studies on atherosclerosis

INTRODUCTION

Cardiovascular disease is one of the most important challenges in modern medicine. Atherosclerotic changes in coronary and peripheral arteries are the main contributors to clinical cardiovascular disease. These arterial changes develop due to a multitude of known and unknown risk factors as well as a patient's individual genetic susceptibility. Atherosclerotic thickening of the arteries precedes the clinical signs and symptoms of cardiovascular disease by years to decades, as illustrated in figure 1. Identifying the patients with increased cardiovascular risk at an early stage and effective modification of the specific risk factors in those patients are key components of preventing cardiovascular complications.

Measurement of carotid vessel wall thickness using high-resolution ultrasound has proven to be an important tool in cardiovascular research. In recent years magnetic resonance imaging (MRI) protocols have been developed to evaluate carotid wall geometry. The most widely used application of both techniques is in the role of intermediate end point in clinical trials. Their use in this capacity has been extensively validated and reviewed. In addition to this application, carotid thickness measurement by ultrasound and MRI has also been used in *in vivo* pathophysiological studies of the atherosclerotic process primarily through associating vessel wall thickness to many non-traditional risk factors.

Despite several decades of experience with carotid imaging in research settings it is not routinely used in clinical practice. Carotid imaging studies could potentially aide clinicians in more accurately identifying patients with high cardiovascular risk. Ultrasound as well as MRI scans can quantify the thickness of the carotid artery wall. Abnormal or premature thickening of the vessel wall is representative of smooth muscular hypertrophy and intimal hyperplasia and are indicative of early atherosclerotic changes. In addition, both imaging modalities are able to detect the presence of atherosclerotic plaques before they cause blood flow changes or stenosis. Therefore these vessel wall measurements carry a great potential benefit for clinicians: they make it possible to identify patients with atherosclerosis at a very early stage, before they exhibit abnormalities on echo duplex examination or angiography. Diagnosing patients with atherosclerosis at such an early stage would allow for timely (lifestyle and pharmacological) interventions , thereby potentially delaying or preventing cardiovascular events in the future. Data from population-based studies as well as clinical trials offer strong arguments for the utilisation of carotid imaging in risk assessment:

- Carotid atherosclerosis can be objectified through non-invasive and highly reproducible techniques (1)
- Carotid thickness and plaques are associated with atherosclerosis in other vascular beds, including the coronaries, cerebral vasculature and other peripheral large arteries. (2), (3) (4) (5)
- Carotid atherosclerosis is independently associated with future cardiovascular events (table 1)
- Data suggests that taking carotid imaging parameters into account improves cardiovascular risk prediction (6)

Nonetheless, the role of carotid imaging in cardiovascular risk assessment has been long debated and overall general consensus is still not reached. Most current clinical guidelines (AHA (7) /ESH (8)/ESC (9)) include some form of recommendation on the use of carotid imaging but they are not uniform and implementation is far from ubiquitous in clinical practice. Several concerns need to be addressed before broad scale implementation can be advised:

- Although ample data is available associating carotid ultrasound abnormalities to elevated cardiovascular risk, imaging protocols are varied and the optimum scanning technique is subject to ongoing debate
- Much of the evidence on carotid MRI abnormalities and increased risk is extrapolated from ultrasound studies and not based on direct long term follow-up studies
- Carotid atherosclerosis has consistently been found to be independently associated with cardiovascular events but the magnitude of the additional predictive power over risk assessment models such as the Framingham risk score and the SCORE model may be marginal. (10) (11) (12) (13)
- Whether treatment decisions based partly on carotid imaging parameters would lead to better outcomes has not been studied.

In this thesis several of the challenges of carotid imaging in clinical practice will be further explored. A summary of the technical considerations on carotid ultrasound and MRI as well as a brief review of the evidence on carotid atherosclerosis and cardiovascular risk will precede the outline of the thesis.

CAROTID ULTRASOUND

Technical considerations

Ultrasound-based measurement of carotid intima-media thickness was first proposed in 1986. (14) It was established that sonographic quantification of the combined thickness of the lamina intima and media of the carotid artery closely approximates microscopic measurement of these arterial structures. Using a high resolution ultrasound device longitudinal images of the carotid artery are obtained. This technique allows visualization of two echogenic lines, separated by an anechoic space. It has been demonstrated that these lines represent the blood-intima and the media-adventitia interfaces. The thickness of this intima-media complex can be measured using computer aided semi-automated edge detection software. Several studies have shown that such an imaging protocol, utilizing high resolution ultrasound and computer aided analysis can produce highly reproducible results. (1) (15) (16) The technique of offline computer aided edge detection was utilized for all the study of this thesis

Ultrasound provides a cross-sectional image of the vessel wall. Figure 2a shows an example of such an image. Because atherosclerosis is often an asymmetrical process, it has been suggested that the ultrasound scans should be performed from several angles of insonation, thereby providing an estimation of the circumferential thickness. (17) Figure 2b is a schematic representation of the different angles of insonation. The parameter of intima-media thickness used in this thesis is an average of the thickness values from four angles at the site of the common carotid artery over a length of one centimeter.

Besides intima-media thickness measurement, ultrasound can also be used to detect the presence of atherosclerotic plaque. The definition of carotid plaque varies in literature. In this thesis the following definition is used: a focal thickening of the intima-media complex of greater than 1.5mm or 1.5 times greater than the surrounding IMT. (18) The plaques can be further classified to be 1) mild if only the aforementioned criteria are met, 2) moderate when encroaching into the arterial lumen and 3) severe if the lesion causes stenosis. Plaque detection was performed under 4 angles of insonation at the site of the common and internal carotid artery and the carotid bulb.

Carotid ultrasound and cardiovascular risk

Accurate identification of patients that are at elevated risk remains challenging for physicians. This is reflected by the observation that in up to 40% of the incident cases of myocardial infarction, the event cannot be explained by the presence of cardiovascular risk factors. (19)

Several large population-based studies have demonstrated that carotid intima-media thickness and the presence of atherosclerotic plaques are independently associated with the occurrence of future cardiovascular events (table 1). It is thought that this association is partly explained by the strong correlation between the severity of carotid atherosclerosis and coronary artery disease. (20) (21) (22) (23) (24)It has been proposed that adding carotid ultrasound parameters to individual patient evaluation strategies may improve the predictive ability of physicians (25) (26) (27) Other studies suggest that adding carotid intima-media thickness values to traditional risk calculating algorithms only modestly improves the predictive strength of the algorithm. (10) (11) (12) (13) (28) The latter findings have led to scepticism about the added benefit of carotid ultrasound parameters. However, these studies were performed on a population-based level, and did not include carotid plaque detection in the analysis. Furthermore, there is evidence that ultrasound-based carotid parameters can improve cardiovascular risk prediction in specific populations, such as hyperlipidemic (29) and hypertensive patients. (30) In summary the potential incremental value of adding vascular parameters, including carotid plaques, to a patient's work-up has not yet been conclusively elucidated, especially in the setting of a secondary referral center as opposed to the general population. Evaluation of these carotid parameters in such a specific patient population (e.g. patients referred to a vascular outpatient department), where these imaging techniques are more readily available is an essential step in facilitating broader application of the technique.

Carotid ultrasound in pathophysiological studies

Another important application of carotid ultrasound is its use as a tool in pathophysiological studies. It is an easy, cost efficient and non-invasive method to assess the association of a broad range of established and potential cardiovascular risk factors to vessel wall thickness and by extension to coronary atherosclerosis and future cardiovascular events. In the last decade numerous articles have been published relating carotid IMT to a wide variety of risk factors such as hyperhomocysteinemia (31), lipoprotein(a) (32), inflammatory cytokines (33), ethnicity (34) (35), endothelial dysfunction (36) and many more. Carotid ultrasound has played a crucial role in advancing our knowledge about human atherosclerosis by allowing *in vivo* studies on the effects of these and other parameters in relatively limited patient numbers.

CAROTID MAGNETIC RESONANCE IMAGING

Technical considerations

Magnetic resonance imaging (MRI) protocols have been developed to measure carotid vessel wall geometry. As opposed to the ultrasound methodology discussed above, MRI images provide a fully circumferential view of the arterial wall. (Figure 3) MRI therefore may have an advantage over ultrasound in measurements of asymmetrical atherosclerotic arteries. The studies reported in this thesis were performed using a 3-Tesla MRI scanner. A dual inversion recovery (black-blood), spoiled segmented k-space fast gradient echo sequence with spectral selective fat suppression was used for the acquisition of the images. This technique has been shown to be highly reproducible and operator independent. (37)

On MRI images of arterial wall thickness the constituent layers cannot be differentiated, unlike ultrasound. Therefore the entire vessel wall thickness is quantified during analysis. These quantifications have also been validated against the golden standard of light microscopic histology, although less extensively than ultrasound based measurement of intima-media thickness. (38) In recent years MRI studies on carotid atherosclerosis have focussed more on plaque burden and composition than on wall thickness and plaque presence as we have done in this thesis. MRI characterization of carotid plaque is a potentially promising technique for clinical risk prediction (39) but has not been used in the studies in this thesis.

Carotid MRI and cardiovascular risk

To date, carotid MRI has mainly been utilized as a surrogate end point in clinical trials. (40) (41) The baseline data in these trials seems to indicate that MRI-based vessel wall parameters are associated with cardiovascular risk factors. However, there are no published data on the association of carotid MRI abnormalities with coronary atherosclerosis or the occurrence of future cardiovascular events. Therefore the role of this technique in cardiovascular risk assessment is currently uncertain. Potentially carotid MRI could prove an important tool, especially in patients with advanced atherosclerosis. These patients often have asymmetrical thickening in the carotid artery that can be overlooked by ultrasound due to the cross-sectional nature of the images. The circumferential view provided by MRI may lead to a more reliable vascular assessment in these patients.

Carotid MRI in pathophysiological studies

There are very few data on the effect of cardiovascular risk factors on MRI-based values of vessel wall thickness. So far, the most important pathophysiological studies have focussed on MRI-based visualization of carotid plaque composition (39) (42) and outward arterial remodelling *in vivo*. (43) Moreover, the inclusion of the lamina adventitia in the MRI-based thickness measurements may facilitate future studies on the role of the outer vascular layer in the atherosclerotic process. Many data from human and animal models suggest an active role for the lamina adventitia. Being able to quantify its thickness through imaging would facilitate *in vivo* studies on this topic. Thus, the main current added value of carotid MRI over ultrasound is its ability to produce fully circumferential images of the entire vessel wall and include the lamina adventitia.

OUTLINE OF THIS THESIS

The main focus of the current thesis has been to explore the role of carotid imaging in clinical cardiovascular risk assessment and pathophysiological studies on atherosclerosis.

A major obstacle for many physicians in general hospitals, preventing the routine use of carotid ultrasound measurements in risk assessment strategies is a lack of the necessary infrastructure. In some clinical centers there are no experienced vascular sonographers. More often, the specialized equipment needed for measurement and analysis of carotid ultrasound scans is absent. To address this issue a study was performed to evaluate the level of accuracy that physicians themselves can achieve when carrying out carotid ultrasound scans during normal clinical practice. Such an office-based method would greatly broaden the scope of carotid ultrasound by allowing every physician to incorporate vascular parameters in their overall cardiovascular risk assessment strategy. The results of the study are reported in **chapter 2**.

Another factor currently limiting the use of carotid ultrasound for risk assessment is the uncertainty of its additive value over traditional risk factors especially in patients with established high cardiovascular risk. This issue is addressed in **chapter 3** by exploring the prevalence of carotid atherosclerosis in the setting of a presumed high-risk population, namely patients referred to a specialized vascular unit for cardiovascular risk management. It is in this setting that carotid ultrasound is readily available, however it can be hypothesized that this specific subset of the general population is at such an increased risk that the ultrasound findings lose their additional predictive power.

Whereas ultrasound-based measurement of carotid wall thickness has been widely validated in large population based studies with clinical outcomes, the potential role of carotid MRI in cardiovascular risk stratification is still largely unknown. In **chapter 4**, the clinical relevance of carotid MRI was explored by comparing MRI measurement of arterial lumen diameter and vessel wall thickness to ultrasound-based measurement. If MRI-based values are equal to ultrasound-based measurements it may be justified to assert that clinical outcome data from ultrasound studies can be extrapolated to MRI-based studies.

It has been demonstrated that ultrasound and MRI do not measure the same part of the arterial wall. Ultrasound quantifies the thickness of the lamina intima and media whereas MRI measures the thickness of the entire vessel wall. This should be taken into account when evaluating pathophysiological studies using these different techniques. The information obtained from ultrasound and MRI may be complementary. In **chapter 5** the different associations of carotid ultrasound and MRI to cardiovascular risk factors is described. In addition, a separate vascular parameter, indicative of adventitia-thickness is proposed using the combination of ultrasound- and MRI-based carotid thickness values.

The development of a reliable method of measuring carotid intima-media thickness has contributed significantly to our understanding of the atherosclerotic process in humans. It has facilitated pathophysiological studies on atherosclerosis *in vivo* in a way that was not possible before. In doing so it has taken a central role in cardiovascular research between the preclinical *in vitro* and animal models and the large epidemiological studies using clinical cardiovascular end-points. **Chapter 6** of this thesis illustrates this point. A literature review about the role of inflammation on atherosclerosis in the setting of diabetes mellitus is presented. The section in the review discussing carotid imaging studies bridges the sections on preclinical studies and clinical end-point studies.

Chapter 7 reports on the findings of a study comparing the effect of cardiovascular risk factors on patients of different ethnicity. While this study represents another example of how carotid ultrasound parameters can be utilized in pathophysiological studies, it also stresses the need for ongoing research with these imaging techniques, particularly in populations of different ethnic origin.

The final chapter **(chapter 8)** of the thesis reviews the literature on carotid ultrasound and risk assessment from the internist's perspective. It provides practical suggestions and recommendations on its use in day-to-day clinical practice. A brief explanation of the key technical aspects and available data from the literature will hopefully help clinicians to decide how and why carotid ultrasound may be of value and in which patients it may be relevant.

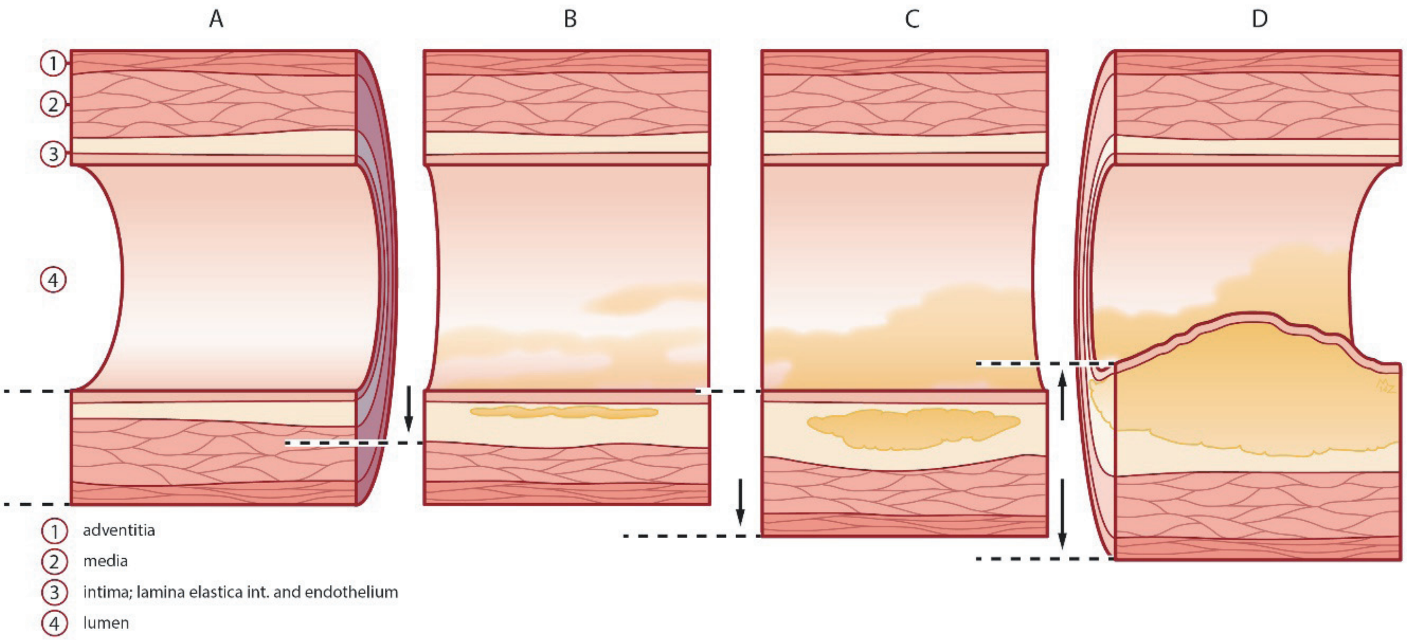

Figure 1 | Schematic representation of the progression of arterial atherosclerosis over a period of decades. Different vascular tests are relavant in the various stages:
A: flow mediated dilatation & pulse wave analyses are aimed at evaluating arterial dysfunction in early stages of disease
B/C: both carotid ultrasound and MRI imaging are able to visualize morphological changes inside the arterial wall, before plaques encroach the lumen
D: invasive intra-arterial contrast and pressure gradient measurements are only useful in advanced disease

FMD: flow mediated dilatation; PWV: pulse wave velocity; PWA: pulse wave analysis; IMT: intima-media thickness; CT: computed tomography; MRI: magnetic resonance imaging

Table 1

Author	n	Follow-up	Carotid parameter	Outcome parameter	Correction for traditional risk factors	HR [95% CI;p-value]]
Salonen et al 1991 (44)	1288	1m-2.5y	Bilateral CCA & BIF	Coronary artery event	none	6.71 [1.33-33.91;p<0.01] stenotic plaque 4.51 [1.51-11.47;p<0.01] minor plaque 2.17 [0.70-6.76;p=NS] increased cIMT
Belcaro et al 1996 (45)	2322	6y	Bilateral CCA, BIF, ICA	Cardiovascular event or death	none	*No formal HR; incident event distribution:* 0% events with normal ultrasound 5.5 % with increased cIMT (p<0.05) 18.4% with minor plaque (p<0.025) 42% with stenotic plaque (p<0.025)
Chambless et al 1997 (46)	14054	10.2y	Bilateral CCA, BIF, ICA	Cardiovascular events or death	Age, gender	5.07 [3.08-8.36;p<0.01] MI in women 8.54 [3.52-20.74;p<0.01] stroke in women 1.87 [1.28-2.69];p<0.01] MI in men 3.62 [1.45-9.15;p<0.01] stroke in men
Bots et al 1997 (47)	7983	2.7y	CCA	Cardiovascular events or death	Age, gender, BMI, smoking BP, lipids, diabetes, prior cardiovascular event	1.38[1.21-1.58;p<0.01] MI 2.23 [1.48-3.36;p<0.01] stroke
O'Leary et al 1999 (48)	5858	6.2y	CCA, ICA	MI, stroke	Age, gender, BP, presence of atrial fibrillation, smoking, diabetes	3.15[2.19-4.52;p<0.01] MI or stroke
Kitamura et al 2004 (49)	1289	4.5y	CCA, BIF, ICA	stroke	Age, BP, BMI	4.8 [1.9-12.0;p<0.01] stroke
Rosvall et al 2005 (50) (51)	5163	7y	CCA	MI, stroke	Age, gender, physical activity, smoking, BP, diabetes, lipids, waist circumference	1.23 [1.07-1.41;p<0.01] MI 1.21 [1.02-1.44;p<0.01] stroke
Lorentz et al 2006 (52)	5056	4.2y	CCA, BIF, ICA	MI, stroke	Age, gender, BMI, BP, lipids, smoking, diabetes	1.85 [1.09-3.15;P<0.01] combined stroke, MI or death
Polak et al 2011 (53)	2965	7.2y	CCA, BIF, ICA	Cardiovascular events or death	Age, gender, BP, lipids, smoking	1.21 [1.13-1.29;p<0.01] per 1SD increase in cIMT 1.92 [1.49-2.47;p<0.01] plaque
Polak et al 2013 (54)	6562	7.8y	CCA, ICA	Cardiovascular events or death	Age, gender, BP, lipids, smoking	1.45 [1.20-1.76;p<0.01] minor plaque 1.65 [1.34-2.03;p<0.01] stenotic plaque 1.33 [1.18-1.49;p<0.01] increased cIMT

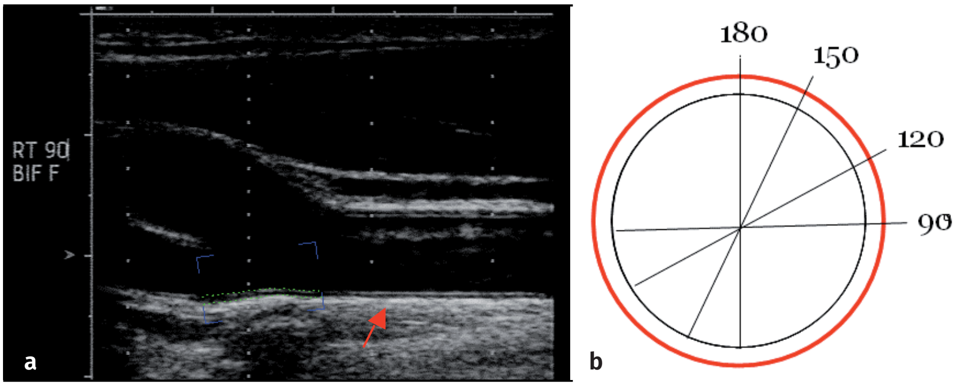

Figure 2a, 2b | Representative example of a longitudinal, cross-sectional carotid ultrasound image of a 62-year old male patient (**a**). Red arrow indicates the intima-media complex in the common carotid artery. The blue box shows an example of a region of interest for computer aided edge detection (green dotted lines). (**b**) Is a schematic representation of a transverse cross-section through the right common carotid artery, illustrating the four angles of insonation at which the carotid artery is examined.

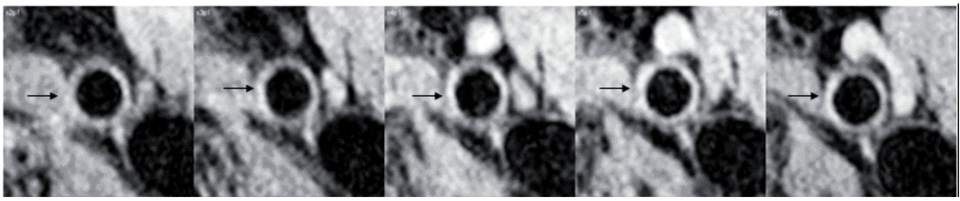

Figure 3 | Representative example of 3-Tesla MRI transverse cross-sectional image of the carotid artery of a 62-year old male subject. Black arrows indicate the carotid artery. Five contiguous transverse slices of 2mm, covering the most distal 1cm of the common carotid artery.

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