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Magnetic resonance imaging of vessel wall morphology and function

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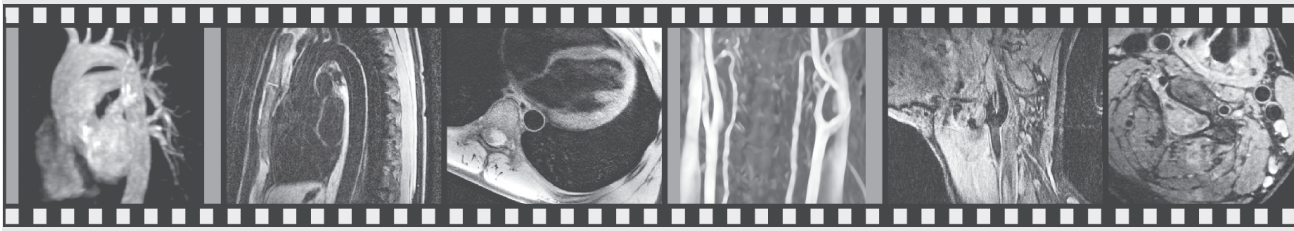
CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS



INTRODUCTION

Cardiovascular disease

Cardiovascular disease and its (thrombotic) complications are the major cause of morbidity and mortality in the industrialized countries (1,2). The majority of cardiovascular disease is caused by atherosclerosis, which is a chronic progressive inflammatory disease that may affect different vascular territories of the arterial system.

Arterial system, normal physiology

The arterial system consists of the aorta and the peripheral arteries. The aorta conducts the blood from the along the arterial tree to perfuse all end-organs. Importantly, the aorta and peripheral arteries can be seen as elastic tubes whose diameter vary with the pulsating pressure from cardiac contraction.

The normal arterial vessel wall consists of three *morphological* distinct layers, the tunica intima, tunica media and the tunica adventitia. The tunica intima consists of a single layer of endothelial cells covering the luminal site of the artery. The tunica media consists of smooth muscle cells with elastic fibers and collagen. Smooth muscle cells have secretory capabilities (i.e. the elastic fibres, collagen fibres, elastic lamellae, and proteoglycans). Elastin fibers are important for maintaining normal pulsatile behavior by allowing the aorta to stretch and distend and the collagen fibers serve as a safety net, preventing the artery from stretching beyond its physiological limit. The tunica media contains varying amounts of elastic fibers and collagen fibers (elastin-collagen ratio) along the arterial system with respect to its site and function *(5)*. The adventitia is a relatively thin connective tissue layer, consisting predominantly of fibroblasts intermixed with smooth muscle cells. The fibroblast also have secretory capabilities (i.e. collagen) (3-5).

In normal physiology, the elastic proximal aorta expands during systole, thereby limiting the transmission of excessive energy towards the various vascular territories and their end-organs. During diastole the aorta recoils thereby facilitating continuous perfusion of the end-organs.

Arterial system, pathophysiology

Genetic and environmental factors may affect both *morphology* (i.e. structure) of the vessel wall and the *function* (i.e. elasticity) of the vessel wall.

Atherosclerotic, *morphologic* changes may affect different sites of the vascular tree, with predilection sites in the coronary arteries, the carotid arteries, and the aorta. Atherogenic risk factors, i.e. smoking, hypertension, and diabetes mellitus impair endothelial function and allow for migration of leucocytes into the vessel wall intima and for the uptake of lipid by macrophages. Progression of atherosclerosis involves migration of smooth muscle cells from the vessel wall media to the vessel wall intima (5). In more advanced lesions, extracellular lipid derived from dead and dying cells accumulates in the central region of a plaque to form a necrotic core. With lesion size progression, ves-

sel wall narrowing occurs. Importantly, lesions with a large lipid core and a thin fibrous overlying cap are at the highest risk for plaque rupture resulting in luminal thrombosis (6). In the coronary arteries progression of atherosclerosis can provoke angina pectoris and plaque rupture mainly resulting in myocardial infarction. In the carotid artery plaque formation may result in a cerebrovascular accident and aortic atherosclerosis may predispose to aneurysm formation or dissection.

Next to the atherosclerotic changes, also the *functional* properties of the vessel wall play an important role in the pathogenesis of cardiovascular disease. Aging interacting with various environmental factors increases the collagen to elastin ratio in the vessel wall media (7), eventually leading to an impaired elasticity of the arterial vessel wall. This impairment may result in deficient absorption of the aortic pulse wave, and causes excessive pulsatile energy to be transmitted from the aorta to the end-organs. For example, excessive pulsatile energy towards the brain might be a factor in the occurrence of cerebrovascular lesions (8,9).

In addition, connective tissue disorders, such as the Marfan Syndrome (MFS) may also cause impaired aortic elasticity (10,11). In the MFS, a genetic abnormality in the fibrillin-1 gene leads to a severe reduction in the amount of fibrilline-1 available to form microfibrils and subsequently an insufficient amount of elastic fibers. Therefore, fibrillin-1 deficiency leads to impaired aortic elasticity. Moreover, fibrillin-1 deficiency results in increased transforming growth factor beta (TGF-β) signaling and smooth muscle cells apoptosis, leading to progressive aortic dilatation (10,11). This may result in aortic dissection and premature death (12).

Increased aortic stiffness is an independent predictor of coronary heart disease and stroke in healthy volunteers and an independent predictor of mortality in the general population, furthermore it is recognized as an important determinant of cardiovascular morbidity and mortality in different patient populations (13-15).

Morphology and function

Both morphologic (i.e. atherosclerosis) and functional (i.e. impaired elasticity) changes of the vessel wall at different sites of the vascular tree play an important role in the development of cardiovascular disease (figure 1). These changes may co-exist, and share underlying mechanisms. Altered functional properties of the vessel wall may influence the development of vessel wall thickening and/or presence of vessel wall thickening itself may increase arterial stiffness. Alternatively, both mechanisms apply and may result in a self-perpetuating process (7,16). For example, in atherosclerosis, the reparative inflammatory process leads to arterial wall calcification and further increase of arterial stiffness (13).

ASSESSMENT OF VESSEL WALL PROPERTIES

Assessment of vessel wall properties can be performed with different invasive and non-invasive imaging techniques; i.e. virtual histology intravascular ultrasound (VH-IVUS),

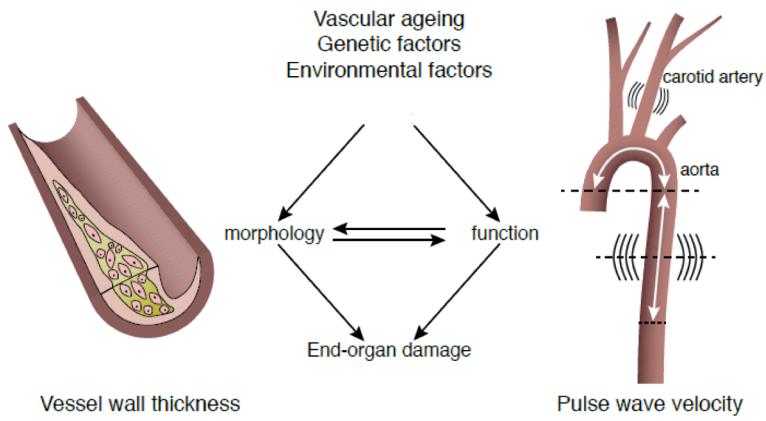


Figure 1. A schematic representation.
Vascular aging, genetic- and environmental factors exert systemic effects on both morphology (i.e. vessel wall thickness) and function (i.e. impaired elasticity) of the arterial vessel wall and play an important role in the development of cardiovascular disease. These changes may co-exist, and share underlying mechanisms. Altered functional properties of the vessel wall may influence the development of vessel wall thickening and/or presence of vessel wall thickening itself may increase arterial stiffness. Alternatively, both mechanisms apply and may result in a self-perpetuating process.

optical coherence tomography (OCT), computed tomography angiography (CTA) and magnetic resonance imaging (MRI). An ideal clinical imaging modality for imaging of vessel wall morphology and function should be safe, non-invasive or minimally invasive, accurate, and reproducible.

In vivo, imaging of vessel wall morphology may be possible using an *invasive* imaging modality, i.e. VH-IVUS. Non-invasively, CTA allows for the assessment of luminal narrowing and to some extent non-invasive evaluation of vessel wall morphology. For wide spread follow-up or surveillance studies, the radiation exposure associated with CTA remains a limitation. Moreover, these modalities are not the first choice for the assessment of vessel wall function.

For the assessment of vessel wall elasticity, applanation tonometry and echo-doppler have extensively been used. However, both modalities only provide an estimation of the *global* aortic elasticity (13). In contrast, the 3D nature of MRI enables an accurate determination of the trajectory length without restrictions regarding imaging planes.

In the last decades, MRI has emerged as a promising non-invasive modality for imaging *both* morphological (i.e. vessel wall thickness) and functional (i.e. vessel wall elasticity) properties of the arterial vessel wall at multiple vascular territories (1). MRI does not involve ionizing radiation; imaging can be repeated sequentially over time and is not hampered by the choice of imaging plane. This thesis will focus on the carotid arteries and the aorta.

IMAGING OF VESSEL WALL MORPHOLOGY

Magnetic resonance imaging at 1.5 Tesla allows for the quantification of carotid artery and aorta vessel wall area and lumen area (17). Moreover, in atherosclerotic disease, a combination of different MR weightings can be used to differentiate between various components of the atherosclerotic plaque (i.e. necrotic core, fibrous tissue and calcium) (17-20). For clinical application a high spatial resolution, derived from an optimal signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR), and a high reproducibility of a multi sequence MRI protocol are warranted. A new generation of high- and ultrahigh-field MR scanners operating at 3T and 7T have recently become available for clinical research (21-24) providing higher SNR and CNR ratios (21,23,25,26). It is expected that vessel wall MR imaging may potentially benefit from imaging at higher magnetic field strengths.

IMAGING OF VESSEL WALL FUNCTION

Pulse wave velocity

Vessel wall function can be determined by measuring vessel wall elasticity. The pulse wave velocity (PWV) is a measure of elasticity of a tube structure (i.e. artery), and is defined as the propagation speed of the pulse waveform or pressure wave along an arterial segment.

PWV is a clinically useful surrogate marker of aortic elasticity (13). Intra-arterially PWV acquired during catheterization is considered to be the most accurate and therefore the gold standard. Non-invasively, PWV-assessment by MRI, using velocity-encoding (VE) is a well-validated method to quantify arterial stiffness (13). Dense temporal and spatial PWV-sampling by two-directional in-plane VE MRI covering the whole aorta in a multi-slice 3-plane volume scan showed high agreement with invasive pressure measurements (8). Importantly, for clinical application, scan time reduction is warranted. Scan time reduction might be possible at the penalty of temporal and spatial sampling density. However, the effect of sampling density on the accuracy of PWV-assessment remains to be investigated.

Furthermore, in MFS and in thoracic aortic aneurysm patients, regional aortic stiffness may be present before aneurysm formation occurs (10,11,27). Regional PWV-assessment with in-plane VE MRI potentially allows for the detection of subtle changes in local aortic stiffness and thereby the identification of these areas at risk (28).

PWV-ratio

Recently it was suggested that not *only* PWV in one artery, i.e. aorta PWV, but the *PWV-ratio* between the aorta PWV and the carotid artery PWV may be a predictor for specific end-organ damage in the brain (13,29,30). It is hypothesized that with ageing and the influence of atherosclerotic risk factors, stiffening of the aorta may be increased

over stiffening of the carotid artery, potentially leading to the transmission of excessive pulsatile energy towards the cerebral microcirculation (7,9,31). In addition to PWV assessment the aorta MRI potentially enables wave propagation sampling along the carotid arterial trajectory from the common carotid artery to the internal carotid artery, thereby allowing for the assessment of carotid artery PWV. Potentially, MRI could be used to explore the differences in PWV of the aorta and the carotid artery and the effect of ageing on the PWV-ratio.

However, assessment of PWV of the carotid artery with VE MRI is challenging due to the need for high temporal resolution and adequate spatial resolution.

IMAGING OF VESSEL WALL MORPHOLOGY AND VESSEL WALL FUNCTION

Detection of changes in vessel wall properties may permit optimized risk stratification, prevention, and early treatment initiation in patients with various degrees of vascular disease (1,6). For example in MFS patients, risk stratification by detection of impaired regional aortic elasticity should be performed to predict aortic dissection. Also, in patients with subclinical atherosclerosis, early treatment initiation may put a hold on arterial wall calcification and the subsequent effect on vessel elasticity. Previously, carotid intima-media thickness measurements have been used as a surrogate marker of generalized atherosclerosis. However, a recent meta-analysis showed that the added value of sampling the common carotid intima-media thickness assessed by ultrasound for 10-year risk prediction of cardiovascular events, in addition to the Framingham Risk Score, was limited (12). It is hypothesized that the interplay between vessel wall morphology and vessel wall function may be site-specific, as age and cardiovascular risk factors exert a different effect on arterial stiffening in various vascular territories (31). MRI potentially allows evaluating the regional association between vessel wall morphology and function within and across vascular territories.

Furthermore, altered mechanical and functional properties are potentially related to end-organ damage (i.e. heart or brain) (9). Indeed, in patients with established atherosclerotic disease, e.g. patients with a previous myocardial infarction, accelerated morphological changes and increased arterial stiffness are considered to be associated. Moreover, atherosclerotic *large* vessel disease is potentially involved in the pathogenesis of cerebral *small* vessel disease (9,31) causing cerebral white matter lesions (WML) to be assessed with MRI (32).

The aim of this thesis is to assess morphological and functional vessel wall properties with various MRI techniques. Improvement of these techniques may be critical for the early detection of changes in vessel wall properties in the future. Advances in vessel wall imaging may allow for a better understanding of the interplay between morphological and functional vessel wall changes over time in various diseases. For potential clinical

application accurate vessel wall imaging might play a role in risk stratification, and might reflect the effect of interventional strategies.

OUTLINE

The present thesis will encompass the following parts, focusing on imaging of vessel wall morphology, imaging of vessel wall function and the combination of morphological and functional vessel wall imaging. Studies are performed in healthy volunteers as well as various patient populations, including MFS patients, thoracic aortic aneurysm patients and patients with a previous myocardial infarction.

The **first part** of this thesis will focus on morphological vessel wall imaging. **Chapter 2** evaluates the scan-rescan reproducibility together with intra- and inter-observer reproducibility of the five MR-sequences of a multi-contrast 3T MRI protocol. In **Chapter 3** the feasibility and potential benefits (in terms of image quality) of moving towards ultrahigh-field 7T MRI carotid artery vessel wall imaging are tested in healthy volunteers.

The **second part** of this thesis will focus on functional vessel wall imaging using MRI. **Chapter 4** investigates the influence of the sampling density on the accuracy of aortic pulse wave velocity from velocity-encoded MRI in patients with marfan syndrome. In **Chapter 5,** the value of MRI-assessed regional pulse wave velocity for predicting absence of regional aorta luminal growth in marfan syndrome is tested. **Chapter 6** describes the MRI-assessed regional pulse wave velocity in patients with thoracic aortic aneurysm. In **Chapter 7** the effect of ageing on the coupling between aortic and carotid PWV is explored.

The **third part** of this thesis will focus on both morphological and functional vessel wall imaging using velocity-encoded MRI. In **Chapter 8,** the association between morphological and functional parameters in the aorta combined with the carotid artery is investigated in a healthy volunteer study. **Chapter 9** describes the associations between carotid VWT and PWV in relation to cerebral white matter lesions in patients with established atherosclerotic disease.

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