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MAGNETIC RESONANCE IMAGING OF VESSEL WALL MORPHOLOGY AND FUNCTION

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The research described in this thesis was carried out at the Departments of Cardiology (Head: Prof. dr. M.J. Schalij) and Radiology (Head: Prof. dr. M.A. van Buchem) of the Leiden University Medical Center.

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MAGNETIC RESONANCE IMAGING OF VESSEL WALL MORPHOLOGY AND FUNCTION

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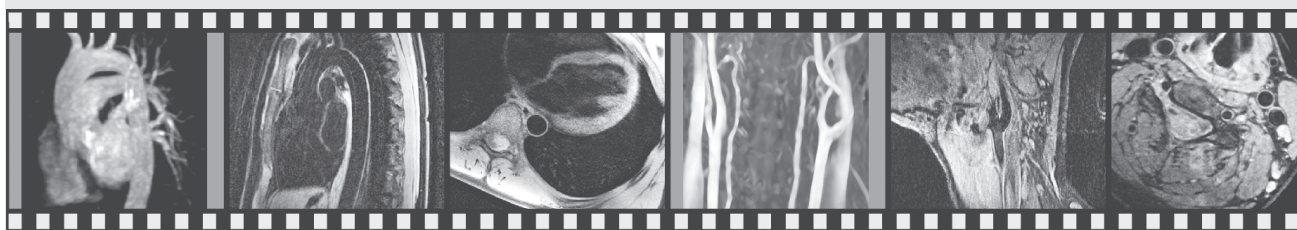
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CHAPTER 1

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 fibrillin-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),

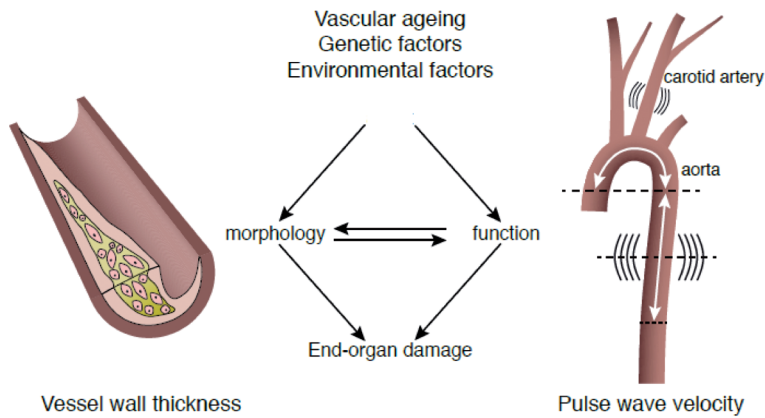


Figure 1. A schematic representation.

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.

REFERENCES

1. Corti R, Fuster V. Imaging of atherosclerosis: magnetic resonance imaging. *Eur Heart J* 2011;32:1709-1719.
2. Lloyd-Jones D, Adams RJ, Brown TM et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* 2010;121:e46-e215.
3. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995;92:657-671.
4. Manning WJ, Pennell DJ. Assessment of the biophysical mechanical properties of the arterial wall. *Cardiovascular magnetic resonance*. 2010.
5. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 2000;20:1262-1275.
6. Schaar JA, Muller JE, Falk E et al. Terminology for high-risk and vulnerable coronary artery plaques. Report of a meeting on the vulnerable plaque, June 17 and 18, 2003, Santorini, Greece. *Eur Heart J* 2004;25:1077-1082.
7. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a “set up” for vascular disease. *Circulation* 2003;107:139-146.
8. King KS, Chen KX, Hulsey KM et al. White matter hyperintensities: use of aortic arch pulse wave velocity to predict volume independent of other cardiovascular risk factors. *Radiology* 2013;267:709-717.
9. Mitchell GF, van Buchem MA, Sigurdsson S et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility—Reykjavik study. *Brain* 2011;134:3398-3407.
10. Dietz HC, Cutting GR, Pyeritz RE et al. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Nature* 1991;352:337-339.
11. Yetman AT, Graham T. The dilated aorta in patients with congenital cardiac defects. *J Am Coll Cardiol* 2009;53:461-467.
12. Murdoch JL, Walker BA, Halpern BL, Kuzma JW, McKusick VA. Life expectancy and causes of death in the Marfan syndrome. *N Engl J Med* 1972;286:804-808.
13. Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness current understanding and future directions. *J Am Coll Cardiol* 2011;57:1511-1522.
14. Laurent S, Boutouyrie P, Asmar R et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001;37:1236-1241.
15. Mattace-Raso FU, van der Cammen TJ, Hofman A et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation* 2006;113:657-663.
16. van Popele NM, Grobbee DE, Bots ML et al. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke* 2001;32:454-460.
17. Cappendijk VC, Cleutjens KB, Kessels AG et al. Assessment of human atherosclerotic carotid plaque components with multisequence MR imaging: initial experience. *Radiology* 2005;234:487-492.
18. Chu B, Phan BA, Balu N, Yuan C, Brown BG, Zhao XQ. Reproducibility of carotid atherosclerotic lesion type characterization using high resolution multicontrast weighted cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2006;8:793-799.
19. Kwee RM, van Engelshoven JM, Mess WH et al. Reproducibility of fibrous cap status assessment of carotid artery plaques by contrast-enhanced MRI. *Stroke* 2009;40:3017-3021.

20. Yuan C, Mitsumori LM, Ferguson MS et al. In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. *Circulation* 2001;104:2051-2056.
21. Niendorf T, Sodickson DK, Krombach GA, Schulz-Menger J. Toward cardiovascular MRI at 7 T: clinical needs, technical solutions and research promises. *Eur Radiol* 2010;20:2806-2816.
22. Umutlu L, Kraff O, Orzada S et al. Dynamic contrast-enhanced renal MRI at 7 Tesla: preliminary results. *Invest Radiol* 2011;46:425-433.
23. van Elderen SG, Versluis MJ, Westenberg JJ et al. Right coronary MR angiography at 7 T: a direct quantitative and qualitative comparison with 3 T in young healthy volunteers. *Radiology* 2010;257:254-259.
24. Vaughan JT, Snyder CJ, DelaBarre LJ et al. Whole-body imaging at 7T: preliminary results. *Magn Reson Med* 2009;61:244-248.
25. Korteweg MA, Veldhuis WB, Visser F et al. Feasibility of 7 Tesla breast magnetic resonance imaging determination of intrinsic sensitivity and high-resolution magnetic resonance imaging, diffusion-weighted imaging, and (1)H-magnetic resonance spectroscopy of breast cancer patients receiving neoadjuvant therapy. *Invest Radiol* 2011;46:370-376.
26. Vaughan JT, Garwood M, Collins CM et al. 7T vs. 4T: RF power, homogeneity, and signal-to-noise comparison in head images. *Magn Reson Med* 2001;46:24-30.
27. Nistri S, Grande-Allen J, Noale M et al. Aortic elasticity and size in bicuspid aortic valve syndrome. *Eur Heart J* 2008;29:472-479.
28. Westenberg JJ, de Roos A, Grotenhuis HB et al. Improved aortic pulse wave velocity assessment from multislice two-directional in-plane velocity-encoded magnetic resonance imaging. *J Magn Reson Imaging* 2010;32:1086-1094.
29. Brandts A, van Elderen SG, Westenberg JJ et al. Association of aortic arch pulse wave velocity with left ventricular mass and lacunar brain infarcts in hypertensive patients: assessment with MR imaging. *Radiology* 2009;253:681-688.
30. van Elderen SG, Brandts A, Westenberg JJ et al. Aortic stiffness is associated with cardiac function and cerebral small vessel disease in patients with type 1 diabetes mellitus: assessment by magnetic resonance imaging. *Eur Radiol* 2010;20:1132-1138.
31. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *J Appl Physiol* 2008;105:1652-1660.
32. Altmann-Schneider I, van der Grond J, Slagboom PE et al. Lower susceptibility to cerebral small vessel disease in human familial longevity: the Leiden Longevity Study. *Stroke* 2013;44:9-14.

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PART I

IMAGING OF VESSEL WALL MORPHOLOGY

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CHAPTER 2

HIGH FIELD CAROTID VESSEL WALL IMAGING: A STUDY ON REPRODUCIBILITY

E.S.J. Kröner, J.J. Westenberg, R.J. van der Geest, N.J. Brouwer, J. Doornbos, M.E. Kooi, E.E. van der Wall, H.J. Lamb, H.J. Siebelink

Eur J Radiol 2013;82:680-5.



ABSTRACT

Purpose: Currently, a multi-contrast protocol, including a combination of five MR-sequences is used as reference standard for morphologic imaging and quantitative measurements of the carotid artery vessel wall. The purpose of this study is to investigate the scan-rescan reproducibility together with intra- and inter-observer reproducibility of each of the five MR-sequences.

Methods: Twenty healthy volunteers (55% male, mean age=26yrs) underwent repeated MR-examinations (3T-Philips-MRI) of the left carotid artery vessel wall with five sequences; T1-TFE, T2-TSE, PD-TSE, T1-TSE and 3D TOF. A standard phased-array coil with two flexible elements of 14×17cm was used to obtain nine transverse imaging sections of the left carotid artery with identical in-plane resolution (0.46×0.46mm²). Reproducibility analysis was performed in 3 slices of the common carotid artery for all sequences.

Results: For, scan-rescan reproducibility, intra class correlation coefficients (ICC) were excellent for all sequences and ranged from 0.79 to 0.95. The intra-observer ICC ranged from 0.89-0.98 and the inter-observer ICC ranged from 0.84-0.96, for both lumen and vessel wall assessment.

Conclusions: By high field MR imaging, vessel wall and lumen area of the carotid artery can be assessed with excellent scan-rescan, intra- and inter-observer reproducibility for all five sequences.

INTRODUCTION

Atherosclerosis is a systemic disease of the vessel wall that affects different vascular territories (e.g. the coronary arteries, the aorta and the carotid arteries), and is the primary cause of heart disease and stroke (1). In the majority of patients presenting with acute vascular events, the underlying cause is atherosclerotic plaque rupture causing luminal thrombosis resulting in occlusion of the artery (2-4). Histopathological studies put forward that the composition of an atherosclerotic lesion has a higher predictive value for an acute vascular event, rather than the degree of luminal narrowing (5). Therefore, early detection of atherosclerosis and specifically identification of high-risk atherosclerotic plaques may permit a better risk-stratification in patients (2). For in-vivo assessment of atherosclerosis, imaging of the carotid arteries is frequently performed (6). Carotid arteries allow easy access, exhibit a larger size, and less motion compared to the coronary arteries (7). Furthermore, it has been shown that carotid atherosclerosis can be considered as a surrogate marker for coronary artery disease and carotid atherosclerosis is associated with cardiac events (8-10).

Carotid artery imaging can be performed with different invasive and non-invasive imaging techniques e.g.: ultrasound (US), intravascular ultrasound (IVUS), computed tomography angiography (CT) and magnetic resonance imaging (MRI). A multi-contrast MRI protocol with a combination of MR-sequences (T1-, T2- and proton-density-weighted (PD) gradient-echo and spin-echo) can be used for vessel wall imaging and to differentiate the various components of the atherosclerotic plaque. A time-of-flight (TOF) sequence can be used for lumen assessment (11). This multisequence MRI protocol, which was developed at 1.5 Tesla, allows accurate assessment of carotid vessel lumen, carotid vessel wall and atherosclerotic plaque composition and was validated to histopathology (12-16). As a result, high-resolution MRI has emerged as the leading non-invasive imaging modality for carotid artery atherosclerosis. Recently, technical development resulted in a multisequence protocol at a higher field strength (3T MRI) and offers significant improvement in signal-to-noise ratio (SNR), wall to lumen contrast-to-noise ratio (CNR) and image quality compared to imaging at 1.5T (17). The merits of 3T carotid atherosclerosis imaging may facilitate translation to clinical applications. Concerning longitudinal follow up of atherosclerosis, repeated MRI scans can be used to detect changes in carotid artery vessel wall [17] and may reflect the effect of interventional strategies (7). Therefore, the use of a multisequence protocol with high reproducibility is crucial in order to detect changes over time.

Only limited data are currently available on the reproducibility of a high field combined multisequence protocol used in carotid vessel wall imaging (18-20). No data are currently available for the reproducibility of the individual MR sequences used in the multisequence protocol at high field MR. Moreover; the use of high-field MRI for clinical follow-up requires knowledge regarding the scan-rescan, intra- and inter-observer reproducibility.

Accordingly, the purpose of the current study is to investigate the scan-rescan reproducibility together with intra- and inter-observer reproducibility of each of the five MR-sequences used in the multisequence MRI protocol at high field (3T).

MATERIALS AND METHODS

Patient population and study protocol

Subjects

Twenty healthy volunteers (eleven men and nine women, mean age: 26 ± 8 years) were included. None of these volunteers had a history of cardiovascular disease. Subjects underwent two repeated MR-examinations consisting of five individual MR-sequences of the left carotid artery vessel wall. After the first examination (scan), subjects were removed from the scanner, the surface coil was removed, and the subjects were then repositioned and the complete examination (rescan) was repeated. All subjects gave informed consent and approval from the local Medical Ethical Committee was obtained.

MR acquisition

MR was performed using a 3T scanner (Achieva, Philips, Best, The Netherlands). A standard Philips SENSE-flex-M surface coil with two flexible elements of 14×17 cm was used. Prior to the multisequence 3T protocol, two sagittal and coronal survey scans were performed to localize the carotid bifurcation. Imaging sequences and planning of the three survey scans were previously described (19). The multisequence 3T protocol was planned on the sagittal and coronal survey scans. The images, consisting of nine transverse slices (thickness 2-mm, interslice gap 0.7mm) were centered at the carotid bifurcation of the left carotid artery.

The multisequence 3T protocol included five sequences which are commonly used in vessel wall imaging. The sequences were applied in the transverse plane with identical in-plane resolution (0.46×0.46 mm²): 2D black-blood (BB) T1-weighted turbo field echo (T1-TFE), 2D BB T2-weighted turbo spin echo (T2-TSE), 2D BB proton-density-weighted TSE (PD-TSE), T1-weighted TSE (T1-TSE), and 3D time-of-flight (TOF) (Table 1, Figure 1).

MR analysis

MR analysis was performed in the left common carotid artery using in-house developed Vessel MASS software (Division of Image Processing, Leiden University Medical Center, Leiden, the Netherlands) (21). The cross-sectional images of the five sequences for scan and rescan, were matched using the bifurcation of the carotid artery as an anatomical landmark. The Vessel MASS software allowed for manual contour definition of luminal and outer wall boundaries. The luminal area was calculated as the area included inside the luminal boundary. The vessel wall area was calculated by subtracting the luminal

Table 1. Scan parameters for the Multi-Sequence 3T Carotid Imaging Protocol.

Parameters	Scan sequences				Time-of-Flight (TOF)
	Black-blood T1-weighted (T1-TFE)	Black-blood T2-weighted (T2-TSE)	Black-blood Proton-Density- weighted (PD-TSE)	Black-blood T1-weighted (T1-TSE)	
Acquisition sequence	TFE	TSE	TSE	TSE	FFE
Acquisition mode	2D	2D	2D	2D	3D
ECG-gated	Yes	Yes	Yes	Yes	No
Echo time (ms)	3.54	50	20	10	3.30
Repetition time (ms)	11.88	2 heartbeats	2 heartbeats	1 heartbeat	26.20
Excitation flip angle (degrees)	45	90	90	90	20
FOV (cm)	14 x 14	14 x 14	14 x 14	14 x 14	14 x 14
Resolution (mm ²)	0.461 x 0.461	0.461 x 0.461	0.461 x 0.461	0.461 x 0.461	0.461 x 0.461
Slice thickness/gap (mm)	2 / 0.7	2 / 0.7	2 / 0.7	2 / 0.7	2.7 / 0
Slices	9	9	9	9	9

Abbreviations: TFE, turbo field echo; TSE, turbo spin-echo; FFE, fast field echo (gradient echo); ECG, Electrocardiography; FOV, field of view

area from the outer contour area. An example of scan and rescan analysis of lumen and vessel wall boundaries for the separate five MR sequences is provided in Figure 2.

Blinded analysis of lumen area and vessel wall area was performed in three slices of the left common carotid artery of which the upper slice was located one slice below the carotid bifurcation. The vessel wall contours were divided in six segments with the centerline method and a maximum vessel wall thickness (MaxTh) was obtained. Then, lumen area, vessel wall area, and MaxTh were calculated, as an average from the three slices in the common carotid artery. To test the scan-rescan reproducibility of the five individual MR-sequences vessel wall and lumen area each of the five sequences were analyzed for scan and rescan by one experienced observer (ESJK, two years of experience in cardiac MRI). To test intra-observer reproducibility, the first scan was analyzed twice for each of the five sequences by the same observer (ESJK). For inter-observer reproducibility, the first scan for each of the five sequences was analyzed by a second observer (NJB, one year experience of cardiac MRI) and compared to the first observer. Both observers were blinded to their own and each other's results.

Statistical analysis

Agreement between repeated measurements (scan-rescan reproducibility intra- and inter-observer reproducibility) was quantified through Intraclass Correlation Coefficient (ICC) for absolute agreement by taking into consideration the variance between observations and subjects. The ICC is the proportion of the total variance caused by the variation between serial measurements or single measures by different observers. Values of 0.75 or greater for ICC were considered excellent agreement, 0.4–0.75 were considered good agreement, and less than 0.4 were considered poor agreement (22).

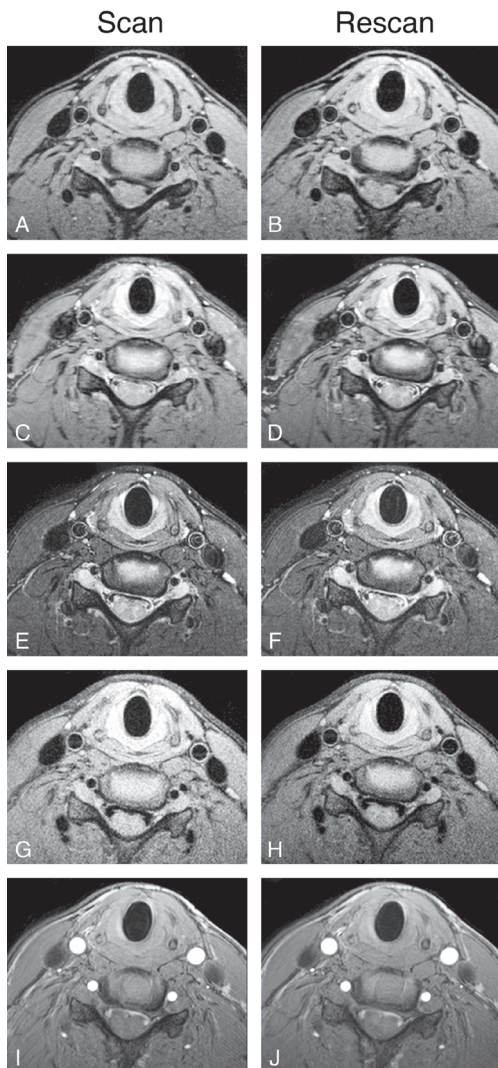


Figure 1. Example of the co-registered contrast images and 3D time-of-flight of two scanning sessions (Scan and Rescan). From top to bottom: **Figure 1A,B:** T1 weighted turbo field echo (T1-TFE); **Figure C,D:** T2 weighted turbo spin echo (T2-TSE); **Figure E,F:** Proton density weighted turbo spin echo (PD-TSE); **Figure G,H:** T1 weighted turbo spin echo (T1-TSE) and **Figure I,J:** time of flight (TOF).

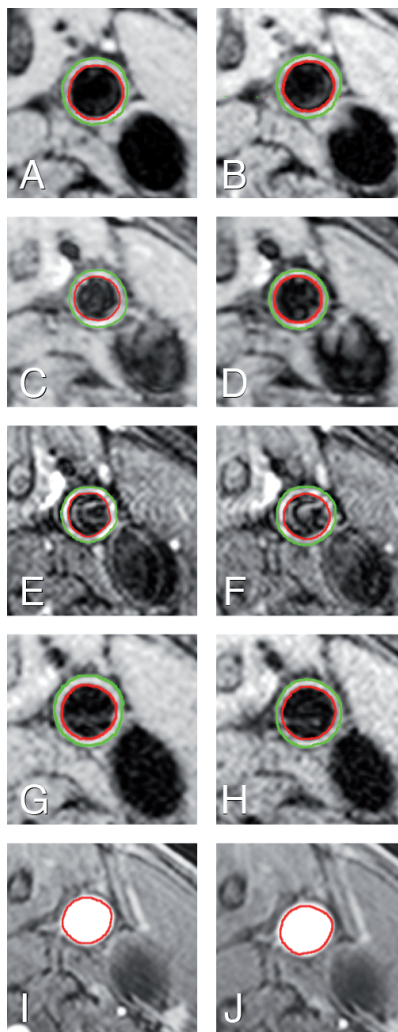


Figure 2. Example of Scan and Rescan analysis of lumen and vessel wall boundaries for the separate five MR sequences. From top to bottom: **Figure 2A,B:** T1-TFE, **Figure C,D:** T2-TSE; **Figure E,F:** PD-TSE; **Figure G,H:** T1-TSE and **Figure I,J:** TOF.

Continuous data are expressed as the mean $\pm$ standard deviation (SD). Mean differences and 95% confidence intervals were determined. Statistical significance was defined at $p < 0.05$). The mean differences between repeated vessel lumen area and vessel wall measurements against the mean value of repeated scans were analyzed with Bland-Altman plots (23). Mean unsigned error of the differences were determined for paired variables. All statistical analyses were performed using SPSS version 18.0 (SPSS, Chicago, IL).

RESULTS

All 20 healthy volunteers completed the MR examination.

Scan-rescan reproducibility

The results for scan-rescan reproducibility are presented in Table 2. Intra class correlation coefficients (ICC) for luminal and vessel wall areas were all excellent for all sequences and ranging from 0.79 to 0.95 ($p < 0.001$). For MaxTh, the scan-rescan reproducibility was good to excellent, with ICC's ranging from 0.73-0.90 ($p < 0.001$). The differences between the repeated (scan-rescan) lumen area and vessel wall area measurements and the mean value of repeated scans are presented in Bland Altman plots, including limits of agreement (Figure 3). No trend in the differences was observed for scan-rescan reproducibility in the Bland Altman plots. In addition, error between scan and rescan was low for both lumen (mean unsigned error, range: 7-12%) and vessel wall (mean unsigned error, range 7-10%).

Table 2. Scan-Rescan Reproducibility for the Common Carotid Artery.

	Lumen Area (mm ²)		Vessel Wall Area (mm ²)		Max. Wall Thickness (mm)	
	ICC	Mean difference	ICC	Mean difference	ICC	Mean difference
T1-TFE	0.91 (0.80-0.97)	-0.24 (3.71)	0.84 (0.63-0.93)	-0.2 (-3.32)	0.73 (0.44-0.89)	-0.00 (0.13)
T2-TSE	0.95 (0.87-0.98)	-0.5 (3.01)	0.94 (0.85-0.97)	-0.20 (1.93)	0.90 (0.77-0.96)	-0.01 (0.08)
PD-TSE	0.90 (0.77-0.96)	-1.17 (3.89)	0.87 (0.70-0.95)	-0.24 (2.89)	0.77 (0.50-0.90)	0.01 (0.15)
T1-TSE	0.86 (0.68-0.94)	-1.86 (5.59)	0.87 (0.69-0.95)	-1.08 (2.58)	0.79 (0.55-0.91)	-0.02 (0.12)
TOF	0.79 (0.55-0.91)	-0.84 (3.90)				

Data are represented as ICC (95% confidence interval) and mean difference (standard deviation).

Abbreviations: ICC, intraclass correlation coefficient; TSE, turbo spin echo; TFE, turbo field echo (gradient echo); TOF, time of flight.

Intra-observer reproducibility

The statistical results for the intra-observer reproducibility are presented in Table 3. Intra-observer reproducibility was excellent for all MR-sequences with ICC ranging from 0.93-0.98 ($P < 0.001$) for both lumen and vessel wall area. Highest intra-observer

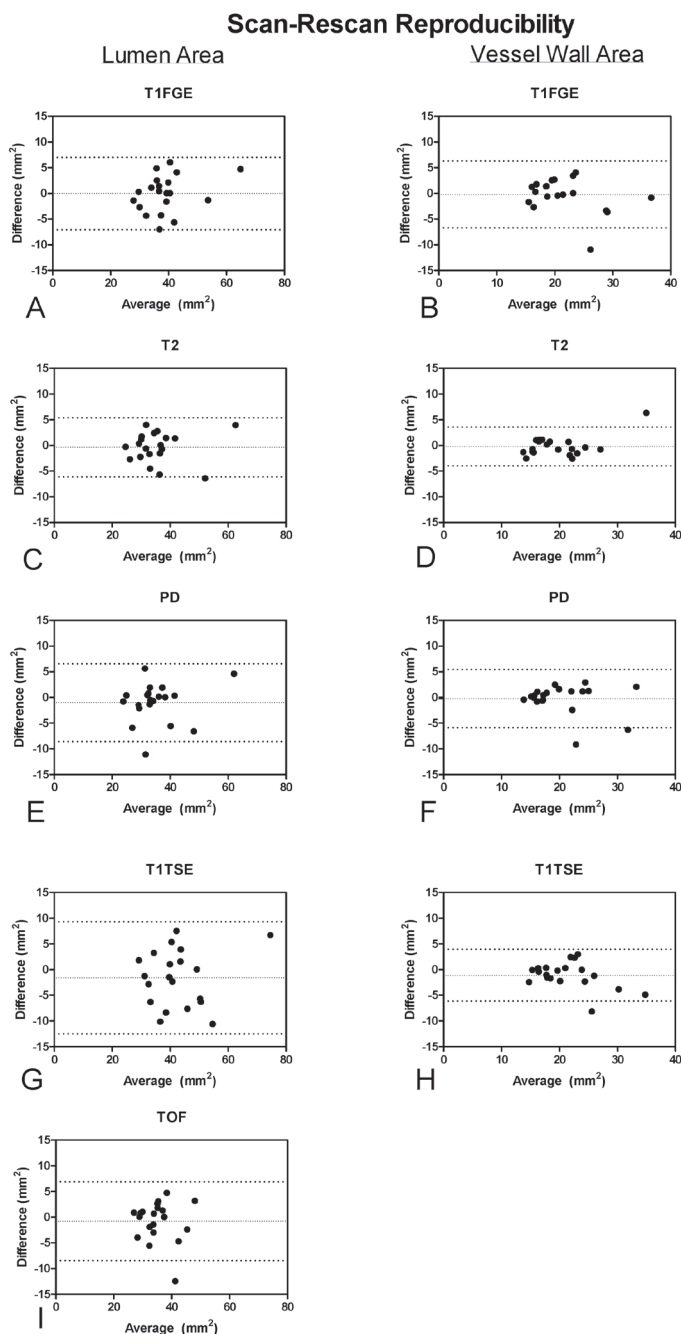


Figure 3. Scan and Rescan reproducibility. Bland-Altman plots for lumen area and vessel wall area; Scan versus Rescan reproducibility for each of the five MR sequences (**Figure 3 A,B:** T1-TFE ; **Figure C,D:** T2-TSE ; **Figure E,F:** PD-TSE ; **Figure G,H:** T1-TSE ; **Figure I:** TOF.) Dashed lines represent the limits of agreement.

reproducibility was found for the T1-TFE (lumen: ICC: 0.98; vessel: ICC: 0.94). For MaxTh, the intra-observer reproducibility of the repeated measurements of maximum vessel wall thickness was good to excellent, with ICC's ranging from 0.65-0.88 ($p < 0.001$). In addition, error between intra-observer measurements was low for both lumen (mean unsigned error, range: 3-5%) and vessel wall (mean unsigned error, range 5-7%).

Table 3. Intra-observer Reproducibility for the Common Carotid Artery.

	Lumen Area (mm ²)		Vessel Wall Area (mm ²)		Max. Wall Thickness (mm)	
	ICC	Mean difference	ICC	Mean difference	ICC	Mean difference
T1-TFE	0.98 (0.96-0.99)	-0.09 (1.49)	0.94 (0.87-0.98)	0.20 (1.88)	0.83 (0.62-0.93)	0.01 (0.09)
T2-TSE	0.97 (0.92-0.99)	0.03 (2.19)	0.89 (0.74-0.95)	-0.33 (2.4)	0.88 (0.72-0.95)	-3E-05 (0.06)
PD-TSE	0.96 (0.91-0.99)	0.46 (1.89)	0.93 (0.84-0.97)	-0.59 (1.57)	0.84 (0.63-0.93)	-0.00 (0.09)
T1-TSE	0.96 (0.90-0.98)	-0.66 (2.9)	0.93 (0.82-0.97)	-0.07(1.66)	0.65 (0.30-0.85)	0.00 (0.1)
TOF	0.96 (0.89-0.98)	0.45 (1.8)				

Data are represented as ICC (95% confidence interval) and mean difference (standard deviation).

Abbreviations: ICC, intraclass correlation coefficient; TSE, turbo spin echo; TFE, turbo field echo (gradient echo); TOF, time of flight.

Inter-observer reproducibility

The statistical results for inter-observer reproducibility are presented in Table 4. Inter-observer reproducibility was excellent for all MR-sequences, for both lumen and vessel wall area. Highest inter-observer reproducibility was found for the T1-TFE (lumen: ICC: 0.96; vessel: ICC: 0.90). The inter-observer reproducibility measurements of MaxTh, reproducibility was good, ranging from ICC 0.69 – 0.84 ($p < 0.001$). In addition, error between inter-observer measurements was low for both lumen (mean unsigned error, range: 3-6%) and vessel wall (mean unsigned error, range 7-11%).

Table 4. Inter-observer Reproducibility for the Common Carotid Artery.

	Lumen Area (mm ²)		Vessel Wall Area (mm ²)		Max. Wall Thickness (mm)	
	ICC	Mean difference	ICC	Mean difference	ICC	Mean difference
T1-TFE	0.96 (0.89-0.98)	0.46 (2.58)	0.90 (0.77-0.96)	-0.14 (2.27)	0.77 (0.52-0.90)	-0.03 (0.10)
T2-TSE	0.93 (0.83-0.97)	0.30 (3.53)	0.93 (0.83-0.97)	-0.25 (2.14)	0.71 (0.41-0.88)	-0.02 (0.12)
PD-TSE	0.93 (0.83-0.97)	0.44 (3.14)	0.94 (0.85-0.97)	-0.23 (1.80)	0.84 (0.63-0.93)	0.00 (0.10)
T1-TSE	0.96 (0.90-0.98)	0.86 (3.03)	0.84 (0.64-0.93)	-0.25 (2.69)	0.69 (0.36-0.86)	-0.01 (0.13)
TOF	0.96 (0.90-0.98)	-0.24(1.70)				

Data are represented as ICC (95% confidence interval) and mean difference (standard deviation).

Abbreviations: ICC, intraclass correlation coefficient; TSE, turbo spin echo; TFE, turbo field echo (gradient echo); TOF, time of flight.

DISCUSSION

The present study evaluated the scan-rescan, intra- and inter-observer reproducibility of carotid vessel lumen and vessel wall assessment of 5 individual sequences (T1-TFE, T2-TSE, PD-TSE, T1-TSE and TOF) of a multisequence imaging protocol at 3T MRI.

Results show that the scan-rescan reproducibility of the separate MR sequences was excellent for all five individual MR sequences. Intra- and interobserver variability was excellent for all five individual MR sequences and T1-TFE showed the highest intra- and interobserver reproducibility for vessel lumen and vessel wall area.

The present study demonstrates an excellent scan-rescan reproducibility of individual MR sequences, which is paramount for serial examination and translation of high-field MR vessel wall imaging into clinical and research applications.

Our study showed that for scan-rescan reproducibility, intra class correlation coefficients (ICC) were excellent for all sequences. In addition error between scan and rescan was low for both lumen (mean unsigned error, range: 8-12%) and vessel wall (mean unsigned error, range 7-10%). The present findings are consistent with a previous 1.5T MR study (including T1, T2 and PD) on measurement precision of the carotid lumen and vessel wall area reporting measurement error ranging from 6-10% for lumen and 11-12% for vessel wall when scans at different time points were compared (14). A previous study from our institution showed also that vessel wall area and lumen area of the carotid artery can be assessed with high scan-rescan reproducibility at 3T, but this study involved only a T1-weighted TFE sequence (19). The reproducibility of the T1-weighted TFE sequence is confirmed by the present study and our data show that this finding also extends to the other sequences of the multisequence 3T imaging protocol. A recent study by Li et al. in which lumen and vessel wall were analyzed based only on the information provided by a reference standard consisting of the combined analysis of all five sequences demonstrated an ICC of 0.94 for total vessel wall volume and 0.99 for lumen volume of the common carotid artery (18). However, no specific data on the reproducibility on the separate MR sequences was provided. Our study provides the lacking information and showed excellent reproducibility of the five individual MR-sequences.

In addition, we also reported intra- and inter-observer reproducibility of the individual MR sequences. Intra- and inter-observer reproducibility was excellent for all MR-sequences, for both vessel wall area and lumen area. Highest intra-observer reproducibility and highest inter-observer reproducibility was found for the T1-TFE sequence. For the measurements of MaxTh, intra- and inter-agreement reproducibility was slightly lower, which could be explained by the fact that this measurement is more susceptible to outliers.

For clinical application, reproducibility of serial non-invasive examination of the carotid lumen and vessel wall is paramount. The present multisequence protocol with excellent scan-rescan reproducibility strongly suggests the possibility for a reliable serial evaluation of carotid lumen and vessel wall. This serial assessment may be particularly useful to evaluate the time course of carotid atherosclerosis and it can serve as

an endpoint to monitor the effect of interventional strategies on carotid atherosclerotic disease. Possibly in the future, the composition of carotid atherosclerosis may influence patient management in clinical practice.

With the present study results, one may even consider using limited MR sequences only for quantitative serial assessment of the vessel lumen and vessel wall area. This minimization of the MR multi-sequence protocol was also proposed by others, since each MR sequence requires additional scan time (24). In the current study, scan-rescan reproducibility T1-TFE and T2-TSE perform best, with a slightly better intra- and inter-observer reproducibility for T1-TFE. Furthermore, the expected development of automated MR analysis methods for vessel lumen and vessel wall may further improve the potential application of MR vessel wall imaging by minimizing errors between repeated scans and different observers (25,26). Further studies are needed to demonstrate if a carotid MRI protocol involving minimization of present 3T MR sequences has the same results in patients with known carotid atherosclerotic disease.

The following limitations need to be acknowledged. This study focused on lumen and vessel wall reproducibility of the left common carotid artery in a relative small study population of healthy volunteers without occlusive plaques. In addition, scan and rescan were performed under stable conditions with the same MR technicians and a limited time interval. Further study is warranted whether a MR protocol involving minimization of present 3T sequences demonstrate the same results in patients. In addition, reproducibility analysis in this study may be influenced by patient motion during image acquisition (27), although patients were positioned in a comfortable but with a fixed position of the neck. Of note, the present study is a single centre study using only one type of MRI scanner and software of vessel wall analysis.

In conclusion, high field carotid vessel wall imaging showed excellent scan-rescan reproducibility and excellent intra- and inter-observer reproducibility for the five individual MR-sequences of a multisequence 3T imaging protocol. Therefore, present multisequence 3T MR protocol could potentially be used for serial assessment of carotid vessel lumen and vessel wall area.

1 REFERENCES

- 2 1. Lloyd-Jones D, Adams RJ, Brown TM et al. Heart disease and stroke statistics—2010 update: a
3 report from the American Heart Association. *Circulation* 2010;121:e46-e215.
- 4 2. Schaar JA, Muller JE, Falk E et al. Terminology for high-risk and vulnerable coronary artery plaques.
5 Report of a meeting on the vulnerable plaque, June 17 and 18, 2003, Santorini, Greece. *Eur Heart*
6 *J* 2004;25:1077-1082.
- 7 3. Shah PK. Mechanisms of plaque vulnerability and rupture. *J Am Coll Cardiol* 2003;41:155-225.
- 8 4. Groen HC, Gijzen FJ, van der Lugt A et al. Plaque rupture in the carotid artery is localized at the
9 high shear stress region: a case report. *Stroke* 2007;38:2379-2381.
- 10 5. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death:
11 a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler*
12 *Thromb Vasc Biol* 2000;20:1262-1275.
- 13 6. de Groot E, Jukema JW, Montauban van Swijndregt AD et al. B-mode ultrasound assessment of
14 pravastatin treatment effect on carotid and femoral artery walls and its correlations with coronary
15 arteriographic findings: a report of the Regression Growth Evaluation Statin Study (REGRESS). *J*
16 *Am Coll Cardiol* 1998;31:1561-1567.
- 17 7. Corti R, Fuster V. Imaging of atherosclerosis: magnetic resonance imaging. *Eur Heart J*
18 2011;32:1709-1719.
- 19 8. Lekakis JP, Papamichael C, Papaioannou TG et al. Intima-media thickness score from carotid and
20 femoral arteries predicts the extent of coronary artery disease: intima-media thickness and CAD.
21 *Int J Cardiovasc Imaging* 2005;21:495-501.
- 22 9. Chambless LE, Heiss G, Folsom AR et al. Association of coronary heart disease incidence with
23 carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities
24 (ARIC) Study, 1987-1993. *Am J Epidemiol* 1997;146:483-494.
- 25 10. Hodis HN, Mack WJ, LaBree L et al. The role of carotid arterial intima-media thickness in predicting
26 clinical coronary events. *Ann Intern Med* 1998;128:262-269.
- 27 11. Kwee RM, van Oostenbrugge RJ, Prins MH et al. Symptomatic patients with mild and moderate
28 carotid stenosis: plaque features at MRI and association with cardiovascular risk factors and statin
29 use. *Stroke* 2010;41:1389-1393.
- 30 12. Cappendijk VC, Cleutjens KB, Kessels AG et al. Assessment of human atherosclerotic carotid plaque
31 components with multisequence MR imaging: initial experience. *Radiology* 2005;234:487-492.
- 32 13. Chu B, Phan BA, Balu N, Yuan C, Brown BG, Zhao XQ. Reproducibility of carotid atherosclerotic le-
33 sion type characterization using high resolution multicontrast weighted cardiovascular magnetic
34 resonance. *J Cardiovasc Magn Reson* 2006;8:793-799.
- 35 14. Kang X, Polissar NL, Han C, Lin E, Yuan C. Analysis of the measurement precision of arterial lumen
36 and wall areas using high-resolution MRI. *Magn Reson Med* 2000;44:968-972.
- 37 15. Saam T, Kerwin WS, Chu B et al. Sample size calculation for clinical trials using magnetic resonance
38 imaging for the quantitative assessment of carotid atherosclerosis. *J Cardiovasc Magn Reson*
39 2005;7:799-808.
- 40 16. Yuan C, Mitsumori LM, Ferguson MS et al. In vivo accuracy of multispectral magnetic resonance
41 imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human
42 carotid plaques. *Circulation* 2001;104:2051-2056.
17. Yarnykh VL, Terashima M, Hayes CE et al. Multicontrast black-blood MRI of carotid arteries: com-
parison between 1.5 and 3 tesla magnetic field strengths. *J Magn Reson Imaging* 2006;23:691-
698.

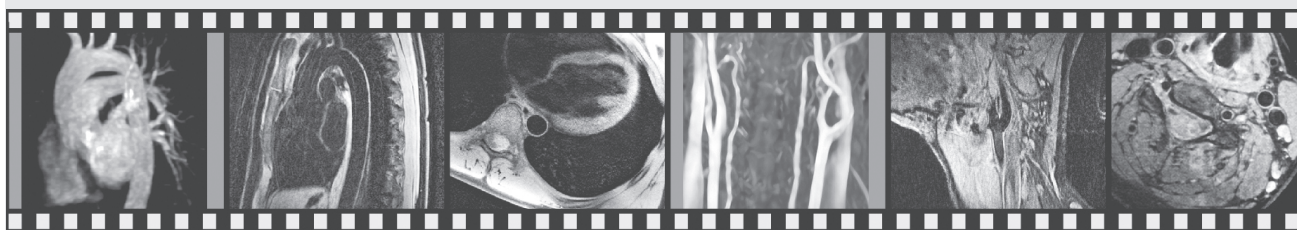
- 1 18. Li F, Yarnykh VL, Hatsukami TS et al. Scan-rescan reproducibility of carotid atherosclerotic plaque
2 morphology and tissue composition measurements using multicontrast MRI at 3T. *J Magn Reson*
3 *Imaging* 2010;31:168-176.
- 4 19. Alizadeh DR, Doornbos J, Tamsma JT et al. Assessment of the carotid artery by MRI at 3T: a study
5 on reproducibility. *J Magn Reson Imaging* 2007;25:1035-1043.
- 6 20. Syed MA, Oshinski JN, Kitchen C, Ali A, Charnigo RJ, Quyyumi AA. Variability of carotid artery
7 measurements on 3-Tesla MRI and its impact on sample size calculation for clinical research. *Int J*
8 *Cardiovasc Imaging* 2009;25:581-589.
- 9 21. Adame IM, van der Geest RJ, Wasserman BA, Mohamed MA, Reiber JH, Lelieveldt BP. Automatic
10 segmentation and plaque characterization in atherosclerotic carotid artery MR images. *MAGMA*
11 2004;16:227-234.
- 12 22. Donker DK, Hasman A, van Geijn HP. Interpretation of low kappa values. *Int J Biomed Comput*
13 1993;33:55-64.
- 14 23. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of
15 clinical measurement. *Lancet* 1986;1:307-310.
- 16 24. Zhao X, Underhill HR, Yuan C et al. Minimization of MR contrast weightings for the comprehensive
17 evaluation of carotid atherosclerotic disease. *Invest Radiol* 2010;45:36-41.
- 18 25. Suinesiaputra A, de Koning PJ, Zudilova-Seinstra E, Reiber JH, van der Geest RJ. Automated quan-
19 tification of carotid artery stenosis on contrast-enhanced MRA data using a deformable vascular
20 tube model. *Int J Cardiovasc Imaging* 2011.
- 21 26. van 't Klooster R, de Koning PJ, Dehnavi RA et al. Automatic lumen and outer wall segmentation
22 of the carotid artery using deformable three-dimensional models in MR angiography and vessel
23 wall images. *J Magn Reson Imaging* 2012;35:156-165.
- 24 27. Balu N, Kerwin WS, Chu B, Liu F, Yuan C. Serial MRI of carotid plaque burden: influence of subject
25 repositioning on measurement precision. *Magn Reson Med* 2007;57:592-599.
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CHAPTER 3

ULTRAHIGH-FIELD 7-T MAGNETIC RESONANCE CAROTID VESSEL WALL IMAGING: INITIAL EXPERIENCE IN COMPARISON WITH 3-T FIELD STRENGTH

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ABSTRACT

Purpose: Magnetic Resonance Imaging (MRI) of the vessel wall enables determination of luminal area, vessel wall thickness, and atherosclerotic plaque characteristics.

For clinical application, high spatial resolution, deriving from optimal signal-to-noise-ratio (SNR) and contrast-to-noise-ratio (CNR) is paramount. Vessel wall MRI is expected to benefit from higher magnetic field strength. Therefore, the purpose of the present study was to develop ultra-high field 7T MRI hardware and protocols for vessel wall imaging of the carotid artery and to compare quantitative parameters of vessel wall morphology and image quality between 3T and 7T MRI.

Methods: 18 volunteers (11 males, 7 females, mean age=29 ± 7 yrs) underwent MRI-examinations at 7T (using a custom built surface transmit/receive coil of 15 cm diameter) and at 3T (using a commercial phased-array coil with two flexible oval elements, each 14 x 17 cm). MRI of the left common carotid artery vessel-wall was performed at 7T with identical in-plane resolution as 3T MRI (0.46 x 0.46 mm²) providing transverse T1- and T2-weighted images. Blinded analysis of morphologic measurements (lumen area and vessel wall area), SNR for vessel wall (SNR_{vw}), and the contrast-to-noise ratio between lumen and wall (CNR) were compared between 7T and 3T.

Results: Morphologic carotid vessel wall measurements were comparable between 7T and 3T for both T1-weighted images (lumen area; ICC: 0.81, vessel wall area; ICC: 0.84) and T2-weighted images (lumen area; ICC: 0.97, vessel wall area; ICC: 0.92). At 7T, SNR_{vw} and CNR were significantly higher as compared to 3T MRI for both T1- (p<0.001) and T2-weighted images (P<0.05), with gain factors ranging from 1.3 to 3.6.

Conclusions: Ultra-high field 7T MR carotid vessel wall imaging is feasible. 7T MRI of the common carotid artery has comparable accuracy for determining luminal area and vessel wall area and has improved SNR_{vw} and CNR as compared to 3T MRI. Therefore, ultra-high field 7T vessel wall MRI may enable more detailed assessment of plaque morphology.

INTRODUCTION

Atherosclerosis and its thrombotic complications are the major cause of morbidity and mortality in the industrialized countries (1). Early detection of atherosclerosis by a non-invasive imaging tool may permit optimized risk-stratification, prevention and early treatment initiation in patients with various degrees of atherosclerotic disease (2). Magnetic resonance imaging (MRI) has emerged as a promising imaging modality for studying atherosclerotic disease in humans in vivo (2).

For clinical application, high spatial resolution, deriving from optimal signal-to-noise-ratio (SNR) and contrast-to-noise-ratio (CNR) is paramount. A new generation of ultra-high field MR scanners operating at 7T has recently become available for clinical research (3-6). In many applications ultra-high field MRI provides higher SNR and CNR, which can be used to increase spatial resolution (3,7-9). Therefore, it is expected that MR imaging of the carotid vessel wall may potentially benefit from higher magnetic field strength.

At present only limited data are available on the feasibility of 7T carotid artery MRI (10). To our knowledge no comparative studies between 3T and 7T carotid artery imaging have been performed investigating vessel morphology measurements (lumen area and vessel wall area) and quantification of image quality (SNR and CNR).

Therefore, the purpose of the present study was to develop an ultra-high field 7T MRI protocol for vessel wall imaging of the carotid artery, and to compare quantitative parameters of vessel wall morphology and image quality between 3T and 7T MRI.

MATERIALS AND METHODS

Patient population and study protocol

Subjects

18 volunteers (11 males, 7 females, mean age=29 ± 7 yrs) were included. None of these volunteers had a previous history of cardiovascular disease. Approval from the local Medical Ethical Committee was obtained and all volunteers gave written informed consent.

General MRI protocol

Subjects underwent MRI examinations of the left carotid artery consecutively on 3T and 7T MR systems. Scanning was performed using commercial 3T and 7T scanners (Achieva, Philips, Best, The Netherlands). The MR systems were equipped with a commercial vector ECG module. The electrodes of the vector were placed on the anterior chest wall, with two electrodes (lead I (L1), L2) in the sternum, one electrode (L3) vertical to L1 and L2, just below the sternum. In addition one electrode (L4) was placed horizontal to L2,

on the left thorax in the mid axillary line (5). All subjects were positioned head first and in the supine position in the scanner.

Similar protocols were employed at both MR field strengths: After acquisition of a three-dimensional (3D) time-of-flight (TOF) sequence to localize the vessel bifurcation, sagittal and coronal 2D survey scans of the left carotid artery were acquired. The multi-contrast carotid vessel wall protocol was planned on these images and consisted of a T1 fast gradient echo (FGE) sequence, a T2 turbo spin echo (TSE) sequence and a 3D TOF sequence. The scan parameters for the multi-contrast protocol at 3T and 7T field strength are given in the next section and an overview is provided in Table 1. The main difference between the T1-weighted protocols at 7T and 3T is that 7T black blood (BB) preparation was performed using local saturation slabs saturating the inflowing venous and arterial blood. In contrast, at 3T BB preparation was performed by a global inversion followed by a slice-selective 10 mm thick re-inversion using the body coil. The difference in BB preparation between 7T and 3T is due to the absence of a body coil at 7T MR system and limited RF coverage of the transmit/receive (T/R) coil at 7T. For the T2-weighted TSE protocols no BB prepulse was used. For the TOF images a saturation slab superior to the imaging stack was placed at 3T, which was not the case at 7T.

Table 1. Scan parameters for Carotid Vessel Wall Imaging Protocols at 3T and 7T

	Black-blood T1-weighted	Black-blood T1-weighted	Black-blood T2-weighted	Black-blood T2-weighted	Time-of- Flight	Time-of- Flight
	3T	7T	3T	7T	3T	7T
Acquisition sequence	FGE	FGE	TSE	TSE	FFE	FFE
Acquisition mode	2D	2D	2D	2D	3D	3D
Echo time (ms)	3.5	3.7	50	50	3.30	3.6
Repetition time (ms)	12.4	13	2 heartbeats	2 heartbeats	26.20	15
Excitation flip angle (degrees)	45	45	90	90	20	20
FOV (mm)	140 x 140	140 x 140	140 x 140	140 x 140	140 x 140	140 x 140
Resolution (mm2)	0.46 x 0.46	0.46 x 0.46	0.46 x 0.46	0.46 x 0.46	0.46 x 0.46	0.46 x 0.46
Slice thickness / gap (mm)	2; 0.7	2; 0.7	2; 0.7	2; 0.7	2; 0.7	2; 0.7

Abbreviations: 3T, 3 Tesla magnetic field strength; 7T, 7 Tesla magnetic field strength; FGE, gradient echo; TSE, turbo segmented spin-echo; FOV, field of view

3T MRI acquisition

RF coil

A standard Philips SENSE-flex-M surface coil with two flexible elements of 14x17cm was positioned around the neck, as previously described (11). An example of coil positioning at 3T and 7T is provided in Figure 1.

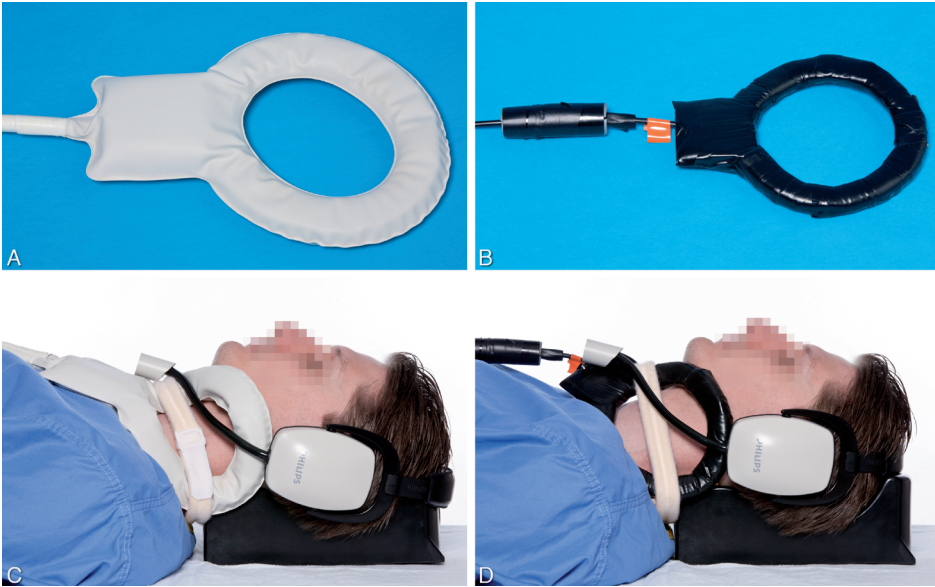


Figure 1. A: Standard Philips SENSE-flex-M surface coil (14 x 17 cm) used for the 3T MR acquisition is shown. B: Custom-built local surface transmit/receive coil of 15-cm diameter used for the 7T acquisition is shown. C: Coil positioning and scanning set-up at 3T MRI. D: Coil positioning and scanning set-up at 7T.

Survey

The 3T protocol has been previously described (11). In short, two survey scans in sagittal and coronal direction were planned on a 3D TOF sequence scout scan.

Multicontrast 3T protocol

Subsequently the multi-contrast 3T protocol, including three sequences were planned on the two surveys scans, perpendicular to the course of the common carotid artery in both views. Nine contiguous transverse slices of 2-mm thickness, with identical in-plane resolution ($0.46 \times 0.46 \text{ mm}^2$), were positioned with the middle of the stack (slice number 5) at the level of the carotid bifurcation of the left carotid artery. The scan parameters were:

1: 2D BB T1-weighted fast gradient echo (FGE) sequence (scan parameters; field-of-view (FOV) 140 x 140 mm, 2.0 mm slice thickness, repetition time (TR): 12.41 ms / echo time (TE): 3.54 ms / flip angle (FA): 45°, acquired pixel size $0.46 \times 0.46 \times 2 \text{ mm}^3$, scan duration per slice = 1.3 minutes at a typical heart rate of 65 beats per minutes, ECG triggering at end-diastole), with up to second order shimming.

2: 2D BB T2-weighted turbo spin echo (TSE) sequence (scan parameters; FOV 140 x 140 mm, 2.0 mm slice thickness, TR / TE / FA: 2 heartbeats/ 50 ms / 90°, acquired pixel size $0.46 \times 0.46 \times 2 \text{ mm}^3$, scan duration per slice = 1.5 minutes at a typical heart rate of 65 beats per minutes, ECG triggering at end-diastole), using linear shimming.

All BB images were obtained with spectral presaturation inversion recovery (SPIR) fat suppression.

3: 3D TOF sequence (scan parameters; FOV: 300 x 300 mm, 2.0 mm slice thickness, TR / TE / FA: 26.20 ms / 3.3 ms / 20°, acquired pixel size 0.46 x 0.46 x 2 mm³, scan duration per slice = 0.4 minutes, acquired without ECG-triggering), using linear shimming.

7T MRI acquisition

RF Coil

A 15-cm diameter local surface T/R surface coil was locally developed. The coil was segmented into six sections by series connected non-magnetic capacitors (American Technical Ceramics). The coil was positioned at the left side of the neck. A cushion was used to fix the position of the neck (Figure 1).

Survey Scans

Three FGE sequence survey scans were performed to facilitate planning of the carotid vessel wall protocol. A 2D TOF sequence was acquired with the following parameters, voxel size = 1 x 1.2 x 5 mm³ and a FOV= 300 x300 mm², 20 transverse slices, TR/ TE/ FA= 7.7 ms / 3.7 ms / 20°, during free breathing and without using ECG triggering. The scan covered 10 cm of the left carotid artery in 38 seconds scan duration. The second survey was planned by defining three points in the center of the common, internal and external carotid arteries, which resulted in an oblique sagittal view of the carotid bifurcation. The third survey was planned in an oblique sagittal plane. The survey scans were acquired using a single slice ECG triggered FGE following parameters: voxel size = 0.46 x 0.47 x 2.5 mm³, FOV = 140 x 140 mm², TR / TE / FA = 12 ms / 3.6 ms / 20°, resulting in an average scan duration of 56 seconds each.

Multi Contrast 7T protocol

Subsequently the multi-contrast 7T protocol, including three sequences were planned on the two surveys scans, perpendicular to the course of the common carotid artery in both views. To ensure registration between 7T and 3T scans, the 7T images, consisting of five contiguous transverse slices of 2-mm thickness, with identical in-plane resolution as 3T (0.46x0.46mm²), were positioned with the top-slice at the level of the carotid bifurcation of the left carotid artery. Acquisition of slices continued in the proximal (caudal) direction covering 1.0 cm of the left common carotid artery.

A localized tip angle calibration was performed as a preparation step before the actual sequences to calibrate the tip angle in the target region (12), and linear shimming was performed in the same region. The scan parameters were:

1: 2D BB T1-weighted FGE sequence (scan parameters: FOV = 140 x 140 mm², TR / TE / FA = 13 ms / 3.7 ms / 45°, scan duration per slice = 1.25 minutes at a typical heart rate of 65 beats per minutes). Three saturation slabs (35 mm thickness), consisting of pairs of manufacturer provided adiabatic RF pulses, were used (two were placed inferior,

and one superior and performed interleaved) to suppress flowing blood after which 8 excitations were performed, with linear profile encoding. The slices were measured sequentially and the saturation slabs followed each slice to obtain optimal blood suppression. Acquisitions were triggered to end diastole.

2: 2D BB T2-weighted fat suppressed TSE sequence (scan parameters: FOV = 140 x 140 mm², TR / TE / FA = 2 heartbeats / 50 ms / 90°, TSE factor = 8, scan duration per slice = 1.2 minutes at a typical heart rate of 65 beats per minutes). Cardiac triggering was performed at end diastole. Fat suppression was performed using a spectrally selective adiabatic inversion pulse to improve the homogeneity of the suppression.

3: 3D TOF sequence (scan parameters: FOV = 140 x 140 mm², TR / TE / FA = 15 ms / 3.6 ms / 20°, scan duration per slice = 0.3 minutes, acquired without ECG-triggering).

MR analysis

The cross-sectional images of the three sequences for the 3T and 7T scans were matched using the bifurcation of the carotid artery as a marker. The 3T and 7T analysis of morphologic measurements and measurements of image quality was performed on one slice of

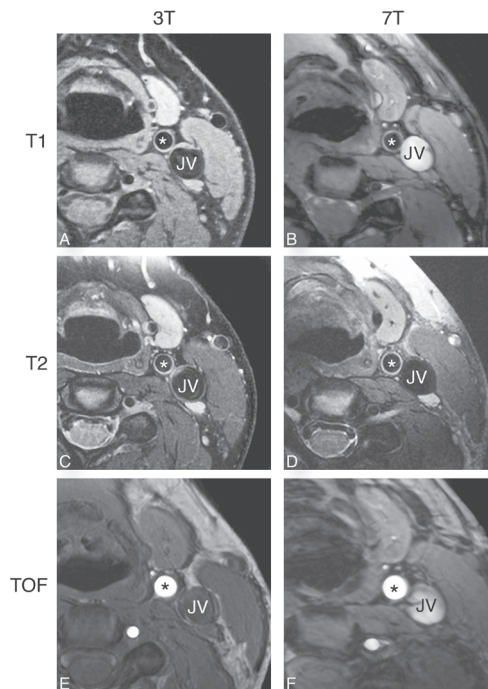


Figure 2. Example of multi-contrast black-blood images (T1- and T2-weighted) and time-of-flight image (TOF) of the left carotid artery obtained on 3T and 7T scanners with identical spatial resolution. From top to bottom: scout, T1-weighted fast gradient echo (T1), T2-weighted turbo spin echo (T2) and time-of-flight (TOF). Asterisks are provided on the transverse slices to indicate vessel lumen.

Abbreviations: 3T, 3 Tesla magnetic field strength; 7T, 7 Tesla magnetic field strength; T1, T1-weighted images; T2, T2-weighted images; TOF, time-of-flight; JV, jugular vein.

the left common carotid artery (4 mm proximal (caudal) to the carotid bifurcation) using Vessel MASS software (Leiden University Medical Center, Leiden, the Netherlands) (13).

Morphological measurements were performed by one observer for each individual sequence (T1- and T2 sequence for lumen area and vessel wall area; TOF sequence for lumen area) for 3T and 7T images (Figure 2). To test intra-observer reproducibility, each scan was analyzed twice by one experienced observer (Observer 1, two years of experience in cardiac MRI). To test inter-observer reproducibility, the scans were analyzed by a second observer (Observer 2, one year experience of cardiac MRI) and data were compared with the first observer.

Measurements of image quality (SNR vessel wall (SNR_{vw}) and CNR lumen/wall) were performed by one observer (Observer 1) for the T1- and T2 sequences. In addition, the SNR_{vw} and CNR were compared between 3T and 7T taking into account the non-gaussian distribution of the signal close to zero (4). SNR was calculated as $SNR = S/\sigma$ (14). S is the true signal intensity corrected for the noise contribution and is obtained by the measured signal (S_m) and the measured background signal (S_n): $S = (S_m^2 - S_n^2)^{1/2}$. The true standard deviation of the noise (σ) depends on the number of receivers. For 7T, when a single single receiver is used the measured standard deviation needs to be divided by 0.655 (11) to obtain σ . Although at 3T two receiver coils were used, the elements are spaced sufficiently apart (left and right side of the neck) such that coupling between the two is negligible. An identical correction factor was therefore applied to the data acquired at 3T and 7T.

CNR was calculated as the difference between vessel wall and lumen SNR: $CNR = SNR_{vessel} - SNR_{lumen}$. Signal intensity from the background noise was sampled by a manually drawn region of interest in the corner of each image, devoid of signal and artifact. Mean signal intensity $\pm$ standard deviation of the vessel wall area and lumen area were provided by the Vessel MASS software.

Statistical analysis

The correlation between morphologic measurements obtained at 3T and 7T MRI was tested with intraclass correlation (ICC) for absolute agreement. ICCs close to 1.0 indicate good agreement between two measurements. The mean differences between repeated measurements against the mean value of repeated scans were described by Bland-Altman plots (15). For the morphological measurements, both intra-observer and inter-observer mean relative errors (MREs) were calculated. For this calculation, the absolute difference between two measurements was calculated per volunteer and divided by the first measurement, to yield the relative error. Consecutively, the mean relative error (MRE) was then calculated.

SNR_{vw} and CNR values are expressed as median (interquartile range). Data from the different measurements were compared using the Wilcoxon signed ranks test for non-parametric paired observations. A p-value < 0.05 was considered statistically significant.

All statistical analyses were performed using SPSS v. 18.0 (SPSS, Chicago, IL).

RESULTS

All 18 volunteers underwent successful MRI scanning at the 3T and 7T MR system.

Lumen and vessel wall.

Figure 2 illustrates example carotid artery imaging of the left common carotid artery from a healthy volunteer at 3T and 7T.

The agreement between 3T and 7T images was calculated using the ICCs. An overview of the calculated ICCs and MRE (%) for the lumen area and vessel wall area is provided in Table 2. Morphologic carotid vessel wall measurements were comparable between 7T and 3T for both T1-weighted images (lumen area; ICC: 0.81, vessel wall area; ICC: 0.84), T2-weighted images (lumen area; ICC: 0.97, vessel wall area; ICC: 0.92) and TOF images (lumen area; ICC: 0.97).

Table 2. Results of Comparison of Morphological Measurements at Matched Location Between 3T and 7T

	3 T	7 T	3T vs 7T	
	Mean (SD) (mm ²)	Mean (SD) (mm ²)	MRE (%)	ICC (CI)
T1 Lumen area	33.16 (6.5)	31.07 (5.88)	5.8	0.85 (0.65; 0.94)
T1 Vessel wall area	17.83 (3.32)	17.17 (3.71)	3.8	0.85 (0.64; 0.94)
T2 Lumen area	33.11 (10.15)	33.28 (8.98)	1.8	0.97 (0.91; 0.99)
T2 Vessel wall area	16.36 (4.58)	16.62 (4.1)	2.8	0.91 (0.78; 0.97)
TOF Lumen area	34.91 (8.39)	34.54 (9.42)	1.5	0.97 (0.91; 0.99)

Abbreviations: 3T, 3 Tesla magnetic field strength; 7T, 7 Tesla magnetic field strength; T1, T1-weighted images; T2, T2-weighted images; TOF, time-of-flight; MRE, mean relative error; ICC, intraclass correlation coefficient.

The mean differences, for lumen and vessel wall area between 3T and 7T measurements are presented (Bland Altman plots) in Figure 3 for both the T1- and T2-weighted images and TOF images. No dependence of the difference vs. the mean was observed.

Furthermore, both intra-observer and inter-observer reproducibility (including ICCs and MRE) for lumen- and vessel wall measurements for both the 3T and the 7T acquisitions was calculated (Table 3). No trend for differences was observed for the intra- and inter-observer reproducibility between the field strengths.

SNR and CNR

Measurements of SNR_{vw} and CNR of the left carotid artery at 3T and 7T are presented in Figure 4. At 7T carotid vessel wall imaging provided a significant increase in SNR_{vw} and CNR for both the T1- ($p < 0.001$) and T2-weighted images ($p < 0.05$). The median gain factor for 7T T1-weighted images was 3.6 for SNR_{vw} and 2.8 for CNR. For T2-weighted images the median gain factor was 1.4 for SNR_{vw} and 1.3 for CNR. Examples ($n=10$) of T1-weighted images and T2-weighted images obtained at 7T are provided in Figure 5.

Agreement of morphological measurements
between 3T and 7T

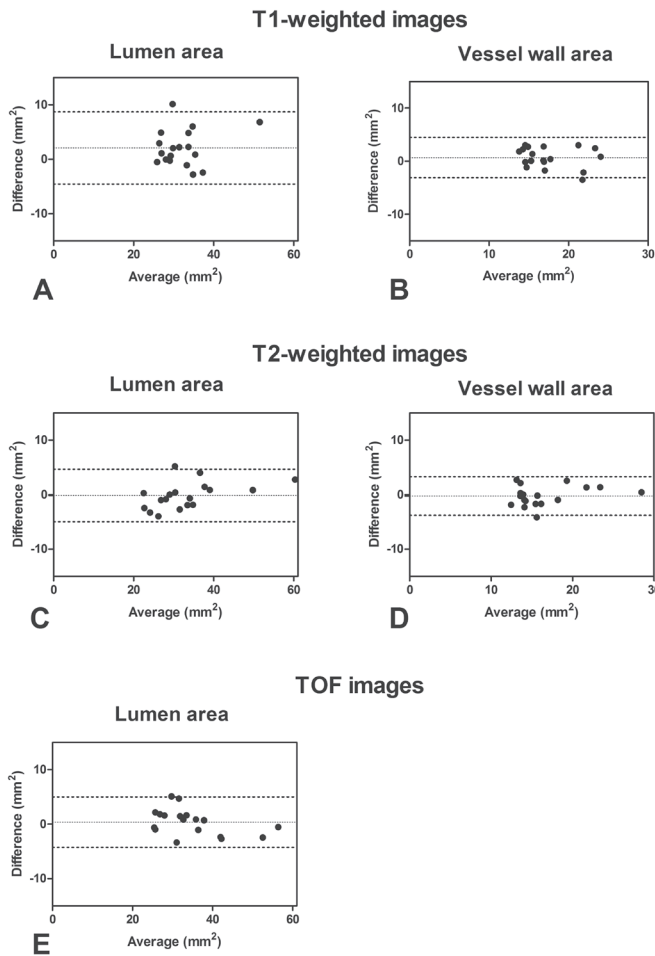


Figure 3. Agreement of morphological measurements between 3T and 7T. Bland-Altman plots for lumen area and vessel wall area, acquired at 3T and 7T, presented for T1- and T2-weighted images and TOF. **Figure 3A,B:** T1-weighted; **Figure C,D:** T2-weighted; **Figure E,** TOF. *Abbreviations:* 3T, 3 Tesla magnetic field strength; 7T, 7 Tesla magnetic field strength; T1, T1-weighted images; T2, T2-weighted images; TOF, time-of-flight.

Table 3. Intra-observer and Inter-observer Reproducibility of Morphologic Measurements

	Observer 1		Observer 1		Intra-observer		Observer 2		Inter-observer	
	Measurement 1	Measurement 2	Mean (SD)(mm ²)	Mean (SD)(mm ²)	MRE %	ICC	Mean (SD) (mm ²)	MRE %	ICC	
3T	T1 Lumen area		33.16 (6.5)	33.26 (6.8)	0.3	0.98 (0.95; 0.99)	33.76 (5.8)	2.6	0.89 (0.73; 0.96)	
	T1 Vessel wall area		17.83 (3.32)	16.68 (1.6)	6	0.76 (0.43; 0.91)	16.86 (2.85)	4.7	0.77 (0.47; 0.91)	
	T2 Lumen area		33.11(10.15)	33.27 (9.46)	1.1	0.99 (0.96; 0.99)	33.05 (8.11)	1.4	0.93 (0.83; 0.97)	
	T2 Vessel wall area		16.36 (4.58)	16.23 (4.37)	0.14	0.93 (0.82; 0.97)	15.75 (3.2)	1.4	0.76 (0.47; 0.90)	
	TOF Lumen area		34.91 (8.39)	34.22 (8.45)	1.8	0.96 (0.90; 0.99)	32.59 (8.65)	6.8	0.93 (0.55; 0.98)	
7T	T1 Lumen area		31.07 (5.88)	30.35 (5.7)	2.2	0.96 (0.89; 0.99)	30.47 (6.6)	2.1	0.92 (0.79; 0.97)	
	T1 Vessel wall area		17.17 (3.71)	17.4 (4.14)	1.5	0.90 (0.75; 0.96)	15.82 (3.09)	6.4	0.66 (0.28; 0.86)	
	T2 Lumen area		33.28 (8.98)	34 (9.7)	2.0	0.98 (0.96; 0.99)	34.37 (9.8)	3.3	0.95 (0.88; 0.98)	
	T2 Vessel wall area		16.62 (4.1)	16.4 (4.1)	1.1	0.96 (0.90; 0.99)	15.2 (3.33)	7.5	0.80 (0.42; 0.93)	
	TOF Lumen area		34.54 (9.42)	34.93 (9.88)	1.1	0.99 (0.96; 1.00)	32.19 (8.73)	6.4	0.92 (0.64; 0.98)	

Abbreviations: 3T, 3 Tesla magnetic field strength; 7T, 7 Tesla magnetic field strength; T1, T1-weighted images; T2, T2-weighted images; TOF, time-of-flight; MRE, mean relative error; ICC, intraclass correlation coefficient.

Comparison of image quality
between 3T and 7T

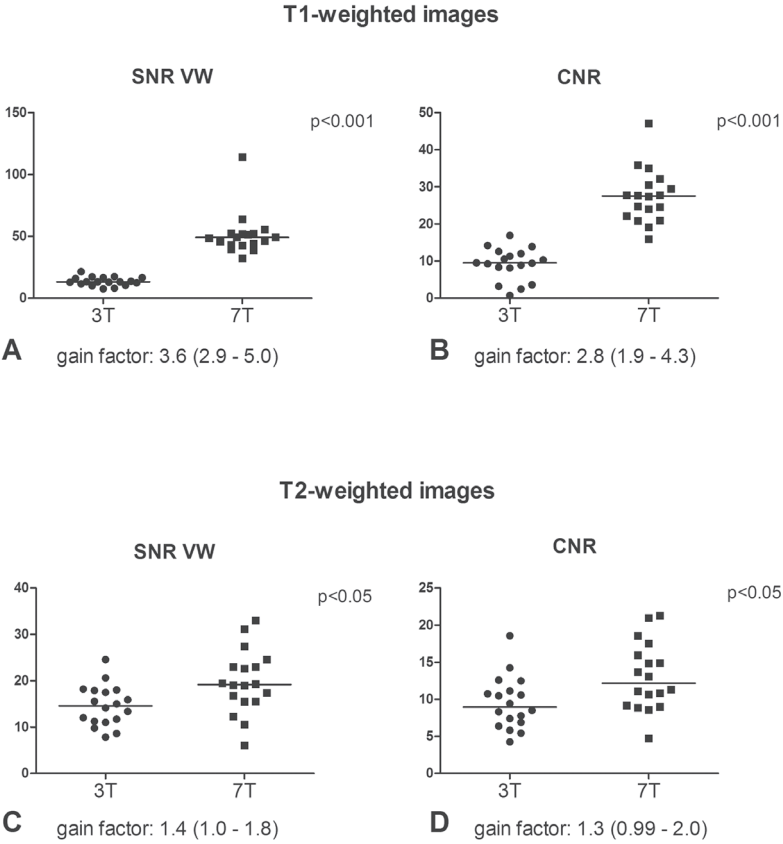


Figure 4. Comparison of image quality between 3T and 7T. Individual measurements are provided of signal-to-noise ratio of the carotid vessel wall (SNR_{VW}) and contrast to noise ratio (CNR) for T1-weighted and T2-weighted images 3T and 7T. **Figure A,B:** T1-weighted; **Figure C,D:** T2-weighted. Individual median gain factor (interquartile range) is provided.
Abbreviations: SNR_{VW} signal-to-noise-ratio for vessel wall; CNR, contrast-to-noise-ratio; 3T, 3 Tesla magnetic field strength; 7T, 7 Tesla magnetic field strength.

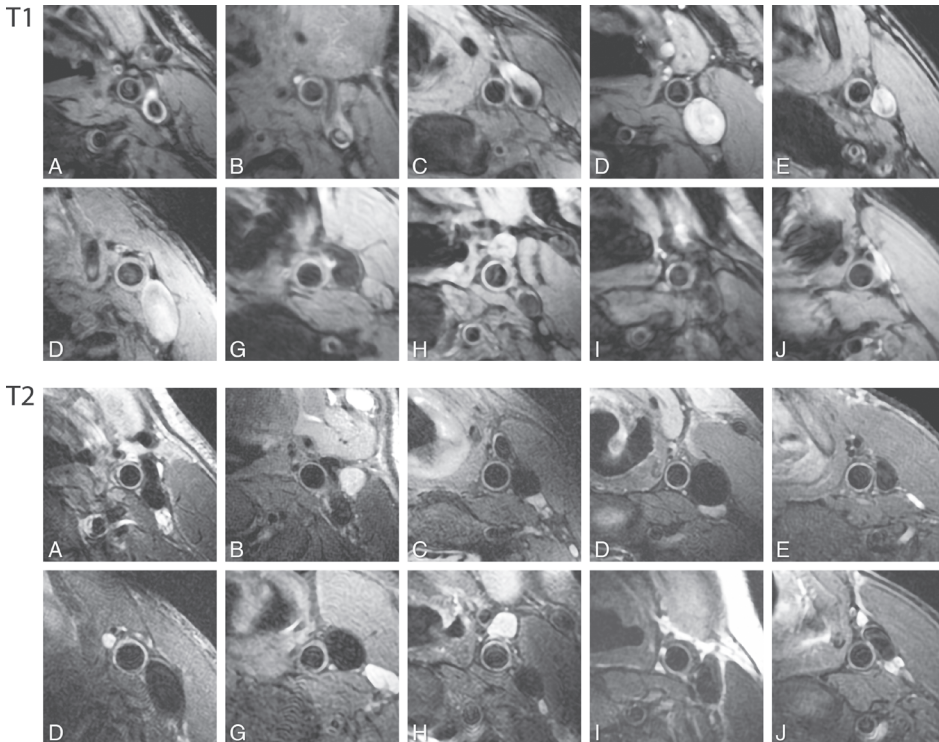


Figure 5. Examples of T1-weighted images and T2-weighted images obtained at 7T. From top to bottom: 10 examples of T1-weighted images (**A to J**) and the corresponding T2-weighted images (**A to J**).
Abbreviations: T1, T1-weighted images; T2, T2-weighted images.

DISCUSSION

The present study, directly compares 3T and 7T carotid vessel wall imaging in healthy volunteers and demonstrates that in vivo carotid vessel wall imaging, with multi contrast protocol is technically feasible at ultra high-field 7T MR equipped with a custom-built RF transmit and receive surface coil. Furthermore, this is the first study comparing morphological measurements and measurements of image quality in a quantitative setting. The main findings of the study are: i) 7T BB common carotid vessel wall imaging, at a predefined position in the common carotid artery relative to the flow divider, is feasible using local saturation slabs, ii) morphologic carotid vessel wall measurements (lumen area and vessel wall area) and intra- and inter-observer reproducibility are comparable between 3T and 7T, iii) ultra high field 7T MRI carotid vessel wall imaging improves SNR_{vw} and CNR compared to 3T.

Our study highlights the potential of 7T carotid MR imaging for assessment of carotid lumen area and vessel wall area, since accurate delineation of the carotid artery vessel wall structure is crucial to detect carotid atherosclerosis and atherosclerotic changes of the vessel wall over time.

A recent study showed initial in vivo results of imaging of the carotid arteries at 7T in three volunteers (10). Estimation of luminal narrowing was performed with high-resolution MRA images, with a non-contrast 3D FLASH sequence. In addition, proton density(PD)/ T2 weighted turbo spin echo images were used for analysis of the carotid vessel wall (10).

The feasibility of carotid vessel wall imaging at 7T is further confirmed by the present study in a larger population and our data show that the feasibility of analysis of the vessel wall also extends to T1-weighted images obtained at 7T.

The present study also provided a comparison of the morphologic measurements at 3T versus 7T. In comparison with previous studies on vessel morphology, the agreement on interscan- and inter-observer reproducibility is in the same magnitude as observed at 3T (11,16).

Carotid vessel wall MRI at 7T is of significant interest because it may provide higher SNR_{vw} and CNR(3). As a consequence spatial resolution can be improved (8). These advances hold potential for more detailed assessment of carotid atherosclerotic plaque morphology (17). The present study provides a direct quantitative comparison for SNR_{vw} and CNR at 3T and 7T. SNR_{vw} and CNR values at 3T were in the same magnitude as previously shown by Underhill et al, comparing carotid vessel wall imaging at 1.5T and 3T (18). At ultra high field strength (7T), improved SNR_{vw} and CNR was observed in our study, both for the T1-weighted gradient echo ($p<0.001$) and for the T2-weighted turbo spin echo images ($P<0.005$). T1-weighted images are the cornerstone for identification of carotid plaque composition and therefore, the significant gains in image quality with median gain factors of 3.6 and 2.8 for SNR_{vw} and CNR respectively, may increase applications to improved carotid vessel wall imaging at ultra high field strength (19,20).

The improved SNR_{vw} and CNR suggest that 7T MRI is a potential technique to assess carotid atherosclerosis in more detail. The vessel wall area is thought to be a surrogate marker for atherosclerotic disease and detailed assessment of carotid atherosclerosis and plaque morphology permits assessment of disease burden (21-23) and identification of vulnerable patients who are at risk of future vascular events (22). A more detailed assessment of atherosclerosis may also permit an increased identification of changes in the carotid artery vessel wall structure over time and can be used to monitor progression of the disease or to monitor intervention (2).

The following limitations need to be acknowledged. Our study focused on the technical feasibility of 7T carotid vessel wall imaging of the common carotid artery in a population of healthy volunteers, without occlusive plaques or reduced flow. Whether carotid vessel wall imaging at 7T MR systems will lead to a better identification of atherosclerosis can not be concluded from the present study and therefore further study is warranted. In addition, 7T imaging of the internal and external carotid artery distal to the carotid bifurcation was not performed. Therefore the results of the present study (including the observed improvement in image quality at 7T) only relate to one slice of the common carotid artery. Further evaluation of the feasibility of carotid vessel wall imaging should

involve; more challenging populations, i.e. patients with extensive carotid plaques, a longer trajectory of the carotid artery, bilateral carotid artery imaging and the development of dedicated coils at 7T. Indeed, carotid imaging is expected to benefit (in terms of penetration depth and image quality) from using more sophisticated transmit array coils as is shown in other applications at high field as well (3,6,10). Kraff et al. showed that when using a multi-element T/R coil at 7T it is possible to image both carotid arteries at the same time; however there are still image inhomogeneities present (10). In the current study, even though the coverage of the local T/R coil was limited, sufficient RF penetration was obtained for adequate visualization of one of the carotid arteries. The RF field was sufficiently homogeneous that with the proper sequence and hardware modification it was possible to achieve the most relevant image contrasts for carotid artery imaging (BB-T1, BB-T2 and TOF). Furthermore, while the design of our 7T feasibility study involved a comparison of 3T and 7T acquisitions, under identical conditions, in the future, the parameters of 7T imaging sequences need to be optimized for time efficiency.

In conclusion, this study shows our initial experience and feasibility of ultra-high field 7T MR carotid vessel wall imaging. Morphologic carotid vessel wall measurements were comparable between 7T and 3T. 7T MRI of the common carotid artery showed improved SNR_{vw} and CNR as compared to 3T MRI. Therefore, ultra-high field 7T vessel wall MRI may permit a more detailed assessment of carotid atherosclerosis and plaque morphology.

1 REFERENCES

- 2 1. Lloyd-Jones D, Adams RJ, Brown TM et al. Heart disease and stroke statistics—2010 update: a
3 report from the American Heart Association. *Circulation* 2010;121:e46-e215.
- 4 2. Corti R, Fuster V. Imaging of atherosclerosis: magnetic resonance imaging. *Eur Heart J*
5 2011;32:1709-1719.
- 6 3. Niendorf T, Sodickson DK, Krombach GA, Schulz-Menger J. Toward cardiovascular MRI at 7 T: clinical
7 needs, technical solutions and research promises. *Eur Radiol* 2010;20:2806-2816.
- 8 4. Umutlu L, Kraff O, Orzada S et al. Dynamic contrast-enhanced renal MRI at 7 Tesla: preliminary
9 results. *Invest Radiol* 2011;46:425-433.
- 10 5. van Elderen SG, Versluis MJ, Webb AG et al. Initial results on in vivo human coronary MR angiog-
11 raphy at 7 T. *Magn Reson Med* 2009;62:1379-1384.
- 12 6. Vaughan JT, Snyder CJ, DelaBarre LJ et al. Whole-body imaging at 7T: preliminary results. *Magn*
13 *Reson Med* 2009;61:244-248.
- 14 7. Korteweg MA, Veldhuis WB, Visser F et al. Feasibility of 7 Tesla breast magnetic resonance imaging
15 determination of intrinsic sensitivity and high-resolution magnetic resonance imaging, diffusion-
16 weighted imaging, and (1)H-magnetic resonance spectroscopy of breast cancer patients receiv-
17 ing neoadjuvant therapy. *Invest Radiol* 2011;46:370-376.
- 18 8. van Elderen SG, Versluis MJ, Westenberg JJ et al. Right coronary MR angiography at 7 T: a direct
19 quantitative and qualitative comparison with 3 T in young healthy volunteers. *Radiology*
20 2010;257:254-259.
- 21 9. Vaughan JT, Garwood M, Collins CM et al. 7T vs. 4T: RF power, homogeneity, and signal-to-noise
22 comparison in head images. *Magn Reson Med* 2001;46:24-30.
- 23 10. Kraff O, Bitz AK, Breyer T et al. A transmit/receive radiofrequency array for imaging the carotid
24 arteries at 7 Tesla: coil design and first in vivo results. *Invest Radiol* 2011;46:246-254.
- 25 11. Alizadeh DR, Doornbos J, Tamsma JT et al. Assessment of the carotid artery by MRI at 3T: a study
26 on reproducibility. *J Magn Reson Imaging* 2007;25:1035-1043.
- 27 12. Versluis MJ, Kan HE, van Buchem MA, Webb AG. Improved signal to noise in proton spectroscopy
28 of the human calf muscle at 7 T using localized B1 calibration. *Magn Reson Med* 2010;63:207-211.
- 29 13. Adame IM, van der Geest RJ, Wasserman BA, Mohamed MA, Reiber JH, Lelieveldt BP. Automatic
30 segmentation and plaque characterization in atherosclerotic carotid artery MR images. *MAGMA*
31 2004;16:227-234.
- 32 14. Yarnykh VL, Terashima M, Hayes CE et al. Multicontrast black-blood MRI of carotid arteries: com-
33 parison between 1.5 and 3 tesla magnetic field strengths. *J Magn Reson Imaging* 2006;23:691-
34 698.
- 35 15. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of
36 clinical measurement. *Lancet* 1986;1:307-310.
- 37 16. Li F, Yarnykh VL, Hatsukami TS et al. Scan-rescan reproducibility of carotid atherosclerotic plaque
38 morphology and tissue composition measurements using multicontrast MRI at 3T. *J Magn Reson*
39 *Imaging* 2010;31:168-176.
- 40 17. Cury RC, Houser SL, Furie KL et al. Vulnerable plaque detection by 3.0 tesla magnetic resonance
41 imaging. *Invest Radiol* 2006;41:112-115.
- 42 18. Underhill HR, Yarnykh VL, Hatsukami TS et al. Carotid plaque morphology and composition: initial
comparison between 1.5- and 3.0-T magnetic field strengths. *Radiology* 2008;248:550-560.
19. Zhao X, Underhill HR, Yuan C et al. Minimization of MR contrast weightings for the comprehensive
evaluation of carotid atherosclerotic disease. *Invest Radiol* 2010;45:36-41.

20. Kwee RM, van Engelshoven JM, Mess WH et al. Reproducibility of fibrous cap status assessment of carotid artery plaques by contrast-enhanced MRI. *Stroke* 2009;40:3017-3021.
21. Zhao XQ, Yuan C, Hatsukami TS et al. Effects of prolonged intensive lipid-lowering therapy on the characteristics of carotid atherosclerotic plaques in vivo by MRI: a case-control study. *Arterioscler Thromb Vasc Biol* 2001;21:1623-1629.
22. Corti R, Fuster V, Fayad ZA et al. Lipid lowering by simvastatin induces regression of human atherosclerotic lesions: two years' follow-up by high-resolution noninvasive magnetic resonance imaging. *Circulation* 2002;106:2884-2887.
23. Corti R, Fuster V, Fayad ZA et al. Effects of aggressive versus conventional lipid-lowering therapy by simvastatin on human atherosclerotic lesions: a prospective, randomized, double-blind trial with high-resolution magnetic resonance imaging. *J Am Coll Cardiol* 2005;46:106-112.

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PART II

IMAGING OF VESSEL WALL FUNCTION

CHAPTER 4

**EVALUATION OF SAMPLING DENSITY ON THE
ACCURACY OF AORTIC PULSE WAVE VELOCITY FROM
VELOCITY-ENCODED MRI IN PATIENTS WITH MARFAN
SYNDROME**

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J Magn Reson Imaging 2012;36:1470-6.



ABSTRACT

Purpose: To evaluate the effect of spatial (i.e. number of sampling locations along the aorta) and temporal sampling density on aortic Pulse Wave Velocity (PWV)-assessment from velocity-encoded MRI in patients with Marfan syndrome (MFS).

Methods: Twenty-three MFS patients (12 men, mean age 36 ± 14 years) were included. Three PWV-methods were evaluated: (1) reference $PWV_{i.p.}$ from in-plane velocity-encoded MRI with dense temporal and spatial sampling; (2) conventional $PWV_{t.p.}$ from through-plane velocity-encoded MRI with dense temporal but sparse spatial sampling at three aortic locations; (3) EPI-accelerated $PWV_{t.p.}$ with sparse temporal but improved spatial sampling at five aortic locations with acceleration by echo-planar-imaging (EPI).

Results: Despite inferior temporal resolution, EPI-accelerated $PWV_{t.p.}$ showed stronger correlation ($r=0.92$ versus $r=0.65$, $p=0.03$) with reference $PWV_{i.p.}$ in the total aorta, with less error (8% versus 16%) and variation (11% versus 27%) as compared to conventional $PWV_{t.p.}$. In the aortic arch, correlation was comparable for both EPI-accelerated and conventional $PWV_{t.p.}$ with reference $PWV_{i.p.}$ ($r=0.66$ versus $r=0.67$, $p=0.46$), albeit 92% scan-time reduction by EPI-acceleration.

Conclusions: Improving spatial sampling density by adding two acquisition planes along the aorta results in more accurate PWV-assessment, even when temporal resolution decreases. For regional PWV-assessment in the aortic arch, EPI-accelerated and conventional PWV-assessment are comparable accurate. Scan-time reduction makes EPI-accelerated PWV-assessment the preferred method-of-choice.

INTRODUCTION

Patients with Marfan syndrome (MFS) have a genetic mutation in the fibrillin-1 gene resulting in increased regional aortic wall stiffening and aortic dilatation (1). Indices of aortic stiffness are prognostically important in MFS patients (2). A surrogate marker of aortic stiffness is aortic Pulse Wave Velocity (PWV), defined as the propagation speed of the systolic velocity wave front through the aorta (3). PWV is a strong predictor of future cardiovascular events and all-cause mortality (4). In MFS patients, PWV assessment is performed in clinical trials that investigated the efficacy of several drugs to attenuate arterial stiffness (5,6). Because of regional variability in aortic wall stiffening in MFS, both global and regional PWV assessment are of clinical importance (7).

Recently, it was shown that 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 (i.e., $PWV_{i,p}$) is the most accurate approach for aortic PWV-assessment with MRI, as it showed high agreement with invasive pressure measurements (8). However, this dense sampling strategy is time-consuming, which is paramount for clinical application. Therefore, one-directional through-plane VE MRI-acquisitions at two locations along the aorta (i.e. $PWV_{t,p}$) (9) is conventionally performed. Sampling with sparse spatial density is considered to represent aortic PWV less accurately as reported correlation with the gold standard was only moderate (9). To ensure adequate temporal resolution – crucial for accurate definition of the transit-time (i.e. the time duration for systolic flow wave to travel between acquisition sites, which defines the PWV) – usually a non-segmented single-readout technique with a relatively long scan time is applied. This long scan time also limits the application of respiratory motion compensation. Accelerating the acquisition by using multiple readouts per echo (e.g. by echo-planar imaging, EPI) will reduce acquisition time and may enable breath-holding. Furthermore, reduction of total acquisition time will enable improvement in spatial sampling density by adding multiple acquisition planes along the aorta within the available examination time. However, this reduction in acquisition time comes at a penalty regarding temporal sampling resolution, as the repetition time will increase with the multiple readouts per echo.

Importantly, the effect of temporal and spatial sampling density on the accuracy of aortic PWV-assessment in patients with MFS remains to be investigated. Therefore, the purpose of this study was to compare conventional $PWV_{t,p}$ to EPI-accelerated $PWV_{t,p}$ against the reference $PWV_{i,p,r}$ both for the total aorta and for the regional PWV assessment in the aortic arch. This study introduces PWV-assessment with sparse temporal but improved spatial sampling by four EPI-accelerated one-directional through-plane VE MRI acquisitions along the aorta, which results in accelerated $PWV_{t,p}$ -sampling at five aortic locations. Of note, the acquisition plane at the level of the pulmonary trunk transects both the ascending aorta and the proximal descending aorta, providing two aortic sampling locations.

MATERIAL AND METHODS

Patient population and study protocol

Twenty-three patients (12 men, 11 women, mean age 36 ± 14 years) with MFS diagnosed according to the Ghent criteria (10), were included. None of these patients had undergone aortic surgery. Patients temporarily refrained from beta-adrenergic blocking medication and were at least 24 hours without medication prior to MRI. All patients gave informed consent and approval from the local Medical Ethical Committee was obtained. Part of the data of this patient group has been published before in a study focusing on age-related PWV (7).

All patients underwent three methods for PWV-assessment by VE MRI; (1) conventional $PWV_{t,p}$ at three aortic locations; (2) EPI-accelerated $PWV_{t,p}$ at five aortic locations; (3) reference $PWV_{i,p}$ covering the full aorta. In Figure 1, a schematic representation of the three PWV-methods is presented.

MRI acquisition

MRI was performed using a 1.5T scanner (Intera, release 12; Philips Medical Systems, Best, the Netherlands). Imaging sequences were previously described (8). In short, after acquisition of a series of thoracic survey images, a three-slice volume slab (covering a para-sagittal view of the aorta) was obtained with a steady-state free precession (SSFP) sequence and used for planning (8). Aortic PWV was subsequently assessed with two one-directional through-plane VE MRI (conventional $PWV_{t,p}$), four accelerated one-directional through-plane VE MRI (EPI-accelerated $PWV_{t,p}$) and two-directional in-plane VE MRI (reference $PWV_{i,p}$).

Conventional $PWV_{t,p}$ at three aortic locations

Two non-segmented k-space sampled, one-directional through-plane VE MRI acquisitions were assessed as shown in Figure 1, B1 (First; at the level of the pulmonary trunk and second; at the abdominal aorta 10cm below the diaphragm) (9). Scan parameters: 90% rectangular field-of-view (FOV)= $300 \times 270 \text{ mm}^2$, 8mm slice thickness, echo time (TE)=2.9ms, repetition time (TR)=4.9ms, flip angle (α)=20°, acquisition voxel size= $2.3 \times 2.1 \times 8.0 \text{ mm}^3$, sampling bandwidth 449Hz, number of signal averages (NSA)=2. Retrospective gating was performed with maximal number of phases reconstructed using view-sharing. The true temporal resolution (TRes, defined as $2 \times \text{TR}$) amounted to 9.8ms. The velocity-sensitivity at the first level was set to 150cm/s and at the second level 100cm/s, respectively. Free breathing was allowed.

EPI-accelerated $PWV_{t,p}$ at five aortic locations

Four one-directional through-plane VE MRI acquisitions were assessed as shown in Figure 1, C1 (first level; aortic valve; second level; pulmonary trunk; third level; diaphragm; fourth level; just above aortic bifurcation). Scan parameters: 90% rectangular FOV= $300 \times 270 \text{ mm}^2$, 8mm slice thickness, TE=6.6ms, TR=12ms, α =20°, acquisition voxel

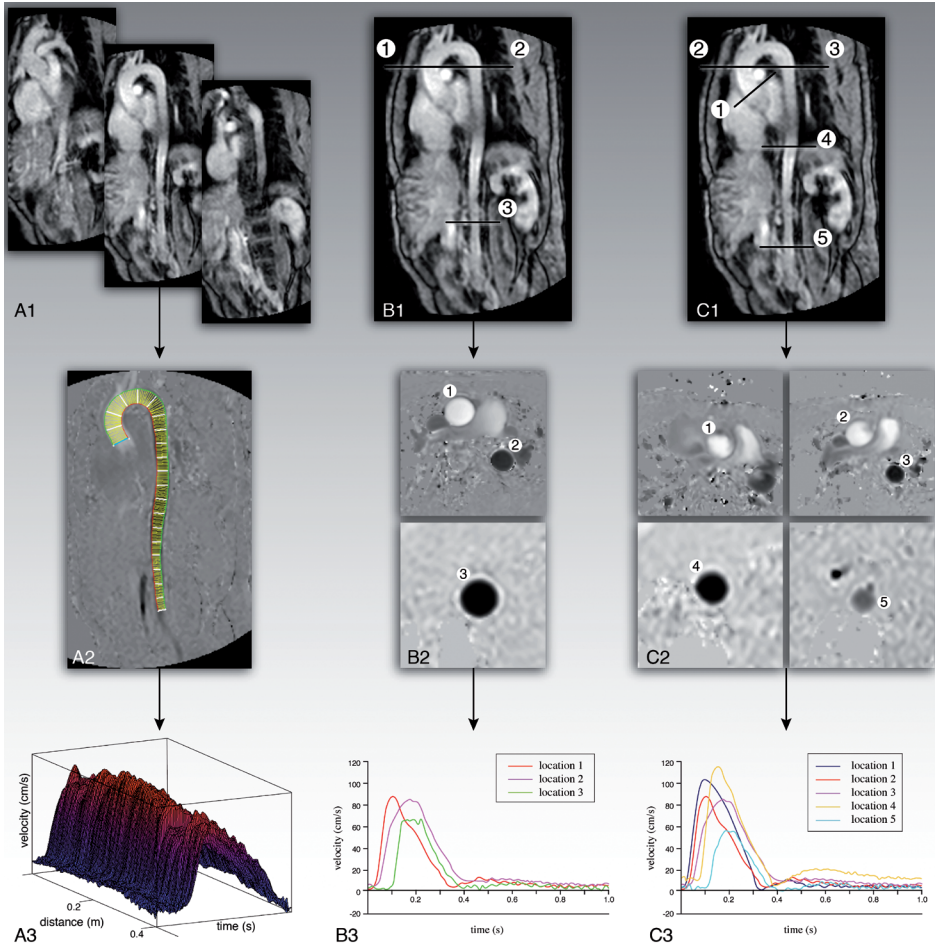


Figure 1. Representation of three methods for aortic PWV-assessment by VE MRI. (A) Reference PWV_{I,p}: dense temporal and spatial sampling. Reference PWV_{I,p} was performed by means of a double-oblique stack of three consecutive slices (A1) with two-directional in-plane velocity-encoding covering the total aorta (A2). The transit-time method was used for the velocity waveforms (A3) to determine the pulse wave velocity at 200 positions along the aortic centre line.

(B) Conventional PWV_{T,p}: dense temporal but sparse spatial sampling. Conventional PWV_{T,p} was performed by 2-slice through-plane velocity-encoded MRI at three aortic locations: (B1) at the level of; the ascending aorta (1), the proximal descending aorta (2) and the abdominal aorta approximately 10cm below the diaphragm (3) with the corresponding phase-velocity images (B2). From the propagation of the resulting velocity waveforms (B3), conventional PWV_{T,p} is determined.

(C) EPI-accelerated PWV_{T,p}: sparse temporal but improved spatial sampling. EPI-accelerated PWV_{T,p} was performed by 4-slice through-plane velocity-encoded MRI at five aortic locations: (C1) at the level of; the aortic root (1), the ascending aorta (2), the proximal descending aorta (3), the diaphragm (4) and just above the aortic bifurcation (5) with the corresponding phase-velocity images (C2). From the propagation of the resulting velocity waveforms (C3), EPI-accelerated PWV_{T,p} is determined.

(Abbreviations: PWV pulse wave velocity; VE velocity-encoded; MRI magnetic resonance imaging; PWV_{T,p} Pulse Wave Velocity from through-plane velocity-encoded MRI; PWV_{I,p} Pulse Wave Velocity from in-plane velocity-encoded MRI).

size= $2.3 \times 2.1 \times 8.0 \text{ mm}^3$, sampling bandwidth 95Hz, NSA=1. Acceleration by commercially-available EPI with EPI-factor 11 was used. This resulted in a longer TR and consequently a lower TRes (i.e., 24ms). Retrospective gating was performed with maximal number of phases reconstructed. The velocity-sensitivity for the first two acquisitions was set to 150cm/s, and for the two distal acquisitions 100cm/s. Breath-holding at end-expiration was performed for each acquisition.

Reference PWV_{i.p.}

Reference PWV_{i.p.} was assessed by two consecutive three-slice two-directional in-plane VE MRI acquisitions (Figure 1, A1) with the full aorta captured in the same volume as acquired with the 3-slice cine SSFP sequence. This method has been described and validated previously (8). In short, velocity-encoding was performed in phase-encoding and frequency-encoding direction consecutively. The velocity-sensitivity was set to 150cm/s. Scan parameters: 60% rectangular FOV= $450 \times 270 \text{ mm}^2$, 10mm slice thickness, TE=2.4ms, TR=4.3ms, $\alpha=10^\circ$, acquisition voxel size= $3.5 \times 2.1 \times 10.0 \text{ mm}^3$, sampling bandwidth 495Hz and NSA=2. Retrospective gating was performed with maximal number of phases reconstructed. TRes amounted to 8.6msec. Free breathing was required.

Image analysis

PWV_{t.p.}

PWV_{t.p.} was determined by the transit-time method (8). The aortic path length (Δx) between subsequent sampling sites was manually determined using MASS software (Leiden University Medical Center, Leiden, The Netherlands), by placing a poly-line along the centerline of the aorta. Wave propagation was evaluated from maximal velocity-time curves that were obtained at each sampling site by using FLOW software (Leiden University Medical Center, Leiden, The Netherlands) with automated contour detection for image segmentation. The foot-to-foot definition was used for transit-time (Δt) assessment, with automated detection of the foot of the systolic velocity wave front (i.e. the wave arrival time) by detecting the intersection point of the horizontal line modeling the constant diastolic flow and a line along upslope of the systolic wave front, modeled by linear regression along 20% to 80% of the range of the flow velocity values along this upslope. PWV, defined as $\Delta x / \Delta t$, was determined by linear regression of the relation between sampling position and wave arrival time.

PWV_{i.p.}

The aorta was manually segmented from the three-slice dataset. The aortic centerline was then automatically determined and 200 equidistantly spaced sampling chords perpendicular to the centerline were defined. The velocity in the direction parallel to the centerline was constructed from the two acquired velocity components. The aortic flow velocity was sampled along each chord to define the maximal velocity per chord. For each chord and each phase, the maximal velocity value over the three slices was

determined (i.e., maximal-velocity-projection), resulting in 200 maximal velocity waveforms. The position along the aortic centerline was determined from a manually traced poly-line in the slab of the three para-sagittal slices. The arrival time of each of the 200 waveforms at their corresponding positions along the aortic centerline was automatically determined similarly as for PWV_{t.p.}-assessment.

Statistical analysis

Image analysis was performed by one observer (in a blinded manner) with more than 15 years experience in cardiac MRI. Conventional PWV_{t.p.} was compared to EPI-accelerated PWV_{t.p.} against the reference PWV_{i.p.}, both for the total aorta and for the aortic arch. Continuous variables are expressed as mean $\pm$ standard deviation (SD). Mean signed and unsigned differences and 95%-confidence interval (95%-CI) were determined for paired variables and the statistical significance of these differences were evaluated using paired t-tests. A significance level $p < 0.05$ was used. The coefficient of variation (COV), defined as the SD of the differences divided by the mean of both measurements, was determined to express variation between measurements. Bland-Altman plots were determined to study systematic differences. Correlation between variables was tested by Pearson correlation coefficient (r). Statistical significance of the difference between correlation coefficients for conventional and accelerated PWV_{t.p.} versus PWV_{i.p.} was tested by stepwise linear regression analysis with PWV_{t.p.} as dependent variable and PWV_{i.p.} and the interaction between PWV_{i.p.} and conventional versus accelerated PWV_{t.p.} as predictors. All statistical analyses were performed using PASW Statistics version 17.0.2 (SPSS, Chicago, IL).

RESULTS

Table 1 summarizes mean heart rate and scan times for all three PWV-methods. The mean length of the evaluated total aorta was 32 ± 4 cm and mean length of the evaluated aortic arch was 12 ± 3 cm.

Table 1. Heart rate and scan times for the three methods for PWV-assessment.

	Heart rate* (bpm)	Total scan time* (minutes)	Scan time per slice* (seconds)
Reference PWV _{i.p.}	66 ± 10	14 ± 2	NA
Conventional PWV _{t.p.}	67 ± 10	7 ± 1	214 ± 34
EPI-accelerated PWV _{t.p.}	66 ± 9	1 ± 0.2	17 ± 2

*Data are represented as mean $\pm$ standard deviation.

Abbreviations: NA: not applicable; PWV_{i.p.}: Pulse Wave Velocity from in-plane velocity-encoded MRI; PWV_{t.p.}: Pulse Wave Velocity from through-plane velocity-encoded MRI

Total Aorta

PWV results for the total aorta are presented in Bland-Altman plots, including limits of agreement (Figure 2, A-B). No obvious trends in the differences were observed. Statistical results are presented in Table 2. EPI-accelerated PWV_{t.p.} showed a significantly stronger correlation ($p=0.03$) with reference PWV_{i.p.} than conventional PWV_{t.p.} ($r=0.92$, $p<0.001$ versus $r=0.65$, $p=0.001$, respectively). Furthermore, as illustrated in the Bland-Altman plot as well as expressed in COV, the variation with reference PWV_{i.p.} is lower for EPI-accelerated PWV_{t.p.} than for conventional PWV_{t.p.} (COV=11% versus COV=27%, respectively). There was no significant difference for either PWV_{t.p.}-method when compared with reference PWV_{i.p.} but the unsigned error for EPI-accelerated PWV_{t.p.} amounted to 8% while 16% for conventional PWV_{t.p.}. Of note, 84% scan time reduction was achieved for EPI-accelerated PWV_{t.p.} when compared to conventional PWV_{t.p.} (1 minute versus 7 minutes).

Table 2. Conventional PWV_{t.p.} and EPI-accelerated PWV_{t.p.} versus reference PWV_{i.p.}

	Total Aorta		Aortic Arch	
	conventional PWV _{t.p.}	EPI-accelerated PWV _{t.p.}	conventional PWV _{t.p.}	EPI-accelerated PWV _{t.p.}
Pearson r	0.65	0.92	0.67	0.66
Difference (m/s)*	0.05±1.68	0.19±0.63	-0.53±1.36	-0.20±1.63
p-value t-test	0.88	0.16	0.07	0.57
Mean unsigned error	16%	8%	18%	21%
Coefficient of variation	27%	11%	24%	28%
Total scan time (seconds)*	428±68	68±10	214±34	17±2

*Data are represented as mean ± standard deviation.
Abbreviations: PWV_{i.p.}: Pulse Wave Velocity from in-plane velocity-encoded MRI; PWV_{t.p.}: Pulse Wave Velocity from through-plane velocity-encoded MRI.

Aortic Arch

PWV results for regional assessment in the aortic arch are presented in Bland-Altman plots (Figure 2, C-D). No obvious trends in the differences were observed. Statistical results are presented in Table 2. Agreement for both PWV_{t.p.}-methods against PWV_{i.p.} was not significantly different ($p=0.46$; conventional PWV_{t.p.}: $r=0.67$, $p<0.001$; EPI-accelerated PWV_{t.p.}: $r=0.66$, $p=0.001$). Also the variation with reference PWV_{i.p.} was comparable for both conventional PWV_{t.p.} and EPI-accelerated PWV_{t.p.} (COV=24% versus COV=28%, respectively). No significant difference for either PWV_{t.p.}-method was present when compared with reference PWV_{i.p.} and unsigned errors were comparable (18% versus 21%, respectively). Of note, 92% scan time reduction was achieved for EPI-accelerated PWV_{t.p.} when compared to conventional PWV_{t.p.} (17 seconds versus 4 minutes).

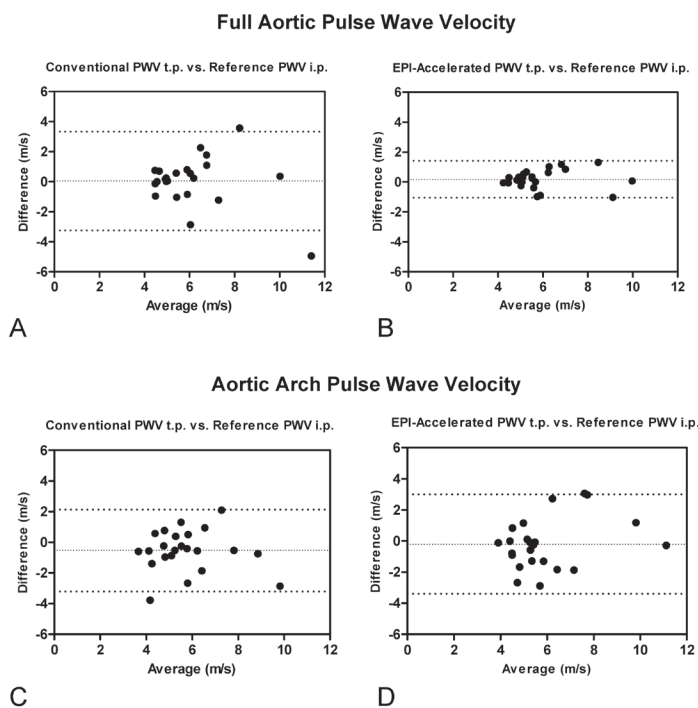


Figure 2. Conventional PWV_{t.p.} and EPI-accelerated PWV_{t.p.} versus reference PWV_{i.p.}, both globally for the total aorta (A,B) and regionally for the aortic arch (C,D). The dashed lines represent the limits of agreement. (Abbreviations: PWV_{t.p.}, Pulse Wave Velocity from through-plane velocity-encoded MRI; PWV_{i.p.}, Pulse Wave Velocity from in-plane velocity-encoded MRI).

DISCUSSION

In this study, the effect of temporal and spatial sampling density on aortic PWV-assessment was evaluated. The main findings are: 1) For global PWV-assessment in the total aorta, EPI-accelerated PWV_{t.p.} with improved spatial sampling at five aortic locations is more accurate than conventional PWV_{t.p.} with sampling at three aortic locations, despite inferior temporal resolution due to EPI-acceleration; 2) For regional PWV-assessment in the aortic arch, EPI-accelerated PWV_{t.p.} is comparable to conventional PWV_{t.p.} with respect to accuracy and variation. Because of the additional 92% scan time reduction, EPI-accelerated PWV_{t.p.} is preferred over conventional PWV_{t.p.}.

It has been reported that dense temporal and spatial PWV-sampling with in-plane VE MRI (in our study used as the standard of reference PWV_{i.p.}) showed higher agreement with invasive pressure measurements, the gold standard for PWV-assessment, and higher reproducibility when compared to conventional PWV_{t.p.} (6). However, PWV_{i.p.}-sampling is time-consuming as acquisition time typically amounts to 15 minutes. Furthermore, image analysis is more elaborate for PWV_{i.p.}-assessment. Therefore, estimations of global

and regional aortic PWV are usually obtained from multi-slice through-plane VE MRI, with the number of acquisition planes along the aorta defining spatial sampling density. Adding acquisition planes along the aorta increases spatial sampling density, but also adds to the total scan time. Applying multiple readouts for a single echo will accelerate scan time but at the cost of decreasing temporal sampling resolution. To our knowledge, the effect of temporal and spatial sampling density on aortic PWV-assessment with VE MRI has not been evaluated yet. In our study, the effect of temporal sampling density is evaluated by comparing single-echo readout with EPI-accelerated multi-echo readout. Conventional $PWV_{t,p}$ showed moderate correlation ($r=0.65$) with the reference $PWV_{i,p,r}$, considerable variation ($COV=27\%$) and a mean unsigned error of 16%. Despite inferior temporal resolution ($T_{Res}=24ms$ instead of $T_{Res}=9.8ms$), improving spatial sampling density by adding two aortic sampling locations significantly ($p=0.03$) improved correlation with reference $PWV_{i,p,r}$ ($r=0.92$) and lowered both variation ($COV=11\%$) and mean unsigned error (8%). Additionally, EPI-accelerated $PWV_{t,p}$ at five aortic locations also resulted in 84% scan time reduction.

In patients with MFS as well as other cardiovascular diseases with regional manifestation of impaired aortic wall stiffening, PWV-assessment at a regional level is of high interest (3). Temporal sampling resolution is a potentially limiting factor defining accuracy of regional PWV-assessment. However, the present study showed that EPI-accelerated $PWV_{t,p}$ -sampling is in comparable good agreement with reference $PWV_{i,p}$ as conventional $PWV_{t,p}$ -sampling, despite almost 2.5-fold inferior temporal sampling resolution. EPI-accelerated $PWV_{t,p}$ -sampling is still advantageous for regional PWV-assessment since it accounts for 92% scan time reduction.

The following limitations need to be acknowledged. This study is a retrospective analysis in a relative small study population. In our study, only MFS patients were investigated and not other patient groups or healthy volunteers. However, regional PWV-assessment is of high interest particularly in this patient population, as PWV-values in the proximal aorta are expected to be increased. Furthermore, the use of EPI-acceleration is another limitation, as it will result in significant errors in velocity values (11). On the other hand, these errors will have minimal influence on PWV-assessment, as this only relies on the ability to assess the transit-time from velocity waveforms and not on accurate velocity assessment. Other acceleration strategies such as parallel imaging or k-t blast can be potentially useful to accelerate acquisition even further (12,13). In addition, breath-holding was performed only during EPI-accelerated $PWV_{t,p}$ -assessment. A previous study by Ley et al. demonstrated the effect of different breathing maneuvers during MRI acquisitions on hemodynamics (14). Since we have not performed a comparison between different breathing maneuvers on PWV measurements, a potential effect of free-breathing versus breath-holding on different PWV-assessments could not be excluded. In this study, only scan time was reported and compared for different PWV-assessments. It should be noted that for positioning additional imaging planes additional examination time is required and depends on the experience of the MRI technician. On the other hand, planning additional acquisition planes can usually be performed during scan time of

1 previous acquisition series and therefore no additional examination time should be
2 required. Finally, for comparison of global aortic PWV_{t,p}-assessment, not identical aortic
3 trajectories were compared. The five aortic sample locations (for EPI-accelerated PWV_{t,p}-
4 assessment) encompassed the aortic trajectory from aortic valve to bifurcation, while
5 conventional PWV_{t,p}-assessment was sampled from ascending aorta to the level 10cm
6 below the diaphragm. For both PWV_{t,p}-assessments, the corresponding aortic trajectory
7 of the reference PWV_{i,p}-assessment was matched for comparison. Furthermore, regional
8 PWV was evaluated in identical aortic trajectory.

9 In conclusion, this study evaluated the effect of temporal and spatial sampling density
10 on PWV-assessment globally in the total aorta and regionally in the aortic arch in pa-
11 tients with MFS using through-plane velocity-encoded MRI. Improving spatial sampling
12 density by adding two acquisition planes along the aorta resulted in more accurate
13 PWV-assessment, even when temporal resolution decreased 2.5-fold by EPI-acceleration.
14 For regional PWV-assessment, EPI-accelerated and conventional PWV-assessment are
15 comparable accurate. Scan time reduction makes EPI-accelerated PWV-assessment the
16 preferred method-of-choice.

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1 REFERENCES

- 2 1. Yetman AT, Graham T. The dilated aorta in patients with congenital cardiac defects. *J Am Coll*
3 *Cardiol* 2009;53:461-467.
- 4 2. Nollen GJ, Groenink M, Tijssen JG, van der Wall EE, Mulder BJ. Aortic stiffness and diameter predict
5 progressive aortic dilatation in patients with Marfan syndrome. *Eur Heart J* 2004;25:1146-1152.
- 6 3. Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness current understanding and
7 future directions. *J Am Coll Cardiol* 2011;57:1511-1522.
- 8 4. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause
9 mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*
10 2010;55:1318-1327.
- 11 5. Forteza A, Evangelista A, Sanchez V et al. [Study of the efficacy and safety of losartan versus
12 atenolol for aortic dilation in patients with Marfan syndrome]. *Rev Esp Cardiol* 2011;64:492-498.
- 13 6. Ahimastos AA, Aggarwal A, D'Orsa KM et al. Effect of perindopril on large artery stiffness and
14 aortic root diameter in patients with Marfan syndrome: a randomized controlled trial. *JAMA*
15 2007;298:1539-1547.
- 16 7. Westenberg JJ, Scholte AJ, Vaskova Z et al. Age-related and regional changes of aortic stiff-
17 ness in the marfan syndrome: Assessment with velocity-encoded MRI. *J Magn Reson Imaging*
18 2011;34:526-531.
- 19 8. Westenberg JJ, de Roos A, Grotenhuis HB et al. Improved aortic pulse wave velocity assessment
20 from multislice two-directional in-plane velocity-encoded magnetic resonance imaging. *J Magn*
21 *Reson Imaging* 2010;32:1086-1094.
- 22 9. Grotenhuis HB, Westenberg JJ, Steendijk P et al. Validation and reproducibility of aortic pulse
23 wave velocity as assessed with velocity-encoded MRI. *J Magn Reson Imaging* 2009;30:521-526.
- 24 10. de Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the
25 Marfan syndrome. *Am J Med Genet* 1996;62:417-426.
- 26 11. Zaitsev M, Hennig J, Speck O. Point spread function mapping with parallel imaging techniques
27 and high acceleration factors: fast, robust, and flexible method for echo-planar imaging distor-
28 tion correction. *Magn Reson Med* 2004;52:1156-1166.
- 29 12. Niendorf T, Sodickson DK. Parallel imaging in cardiovascular MRI: methods and applications. *NMR*
30 *Biomed* 2006;19:325-341.
- 31 13. Beerbaum P, Korperich H, Gieseke J, Barth P, Peuster M, Meyer H. Blood flow quantification in
32 adults by phase-contrast MRI combined with SENSE—a validation study. *J Cardiovasc Magn*
33 *Reson* 2005;7:361-369.
- 34 14. Ley S, Fink C, Puderbach M et al. MRI Measurement of the hemodynamics of the pulmonary
35 and systemic arterial circulation: influence of breathing maneuvers. *AJR Am J Roentgenol*
36 2006;187:439-444.
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- 40
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CHAPTER 5

**MRI-ASSESSED REGIONAL PULSE WAVE VELOCITY FOR
PREDICTING ABSENCE OF REGIONAL AORTA LUMINAL
GROWTH IN MARFAN SYNDROME**

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ABSTRACT

Purpose: In patients with Marfan syndrome (MFS), increased aortic wall stiffening may lead to progressive aortic dilatation. Aortic Pulse Wave Velocity (PWV), a marker of wall stiffness can be assessed regionally, using in-plane multi-directional velocity-encoded MRI. This study examined the diagnostic accuracy of regional PWV for prediction of regional aortic luminal growth during 2-year follow-up in MFS patients.

Methods: In twenty-one MFS patients (mean age 36 ± 15 years, 11 male) regional PWV and aortic luminal areas were assessed by 1.5T MRI. At 2-year follow-up, the incidence of luminal growth, defined as mean luminal diameter increase >2 mm was determined for five aortic segments (S1, ascending aorta; S2, aortic arch; S3, thoracic descending aorta, S4, supra-renal and S5, infra-renal abdominal aorta). Regional PWV at baseline was considered increased when exceeding age-related normal PWV (healthy volunteers ($n=26$; mean age 30 ± 10 years, 15 male)) by two standard-errors. Sensitivity and specificity of regional PWV-testing for prediction of regional luminal growth were determined.

Results: Regional PWV at baseline was increased in 17 out of 102 segments (17%). Significant luminal growth at follow-up was reported in 14 segments (14%). The specificity of regional PWV-testing was $\geq 78\%$ for all aortic segments, sensitivity was $\leq 33\%$.

Conclusions: Regional PWV was significantly increased in MFS patients as compared to healthy volunteers within similar age range, in all aortic segments except the ascending aorta. Furthermore, regional PWV-assessment has moderate to high specificity for predicting absence of regional aortic luminal growth for all aortic segments in MFS patients.

INTRODUCTION

Marfan syndrome (MFS) is an autosomal connective tissue disease caused by mutations in the gene encoding for fibrillin-1 (1). In MFS patients, fibrillin-1 deficiency leads to impaired aortic elasticity (i.e. aortic stiffness), increased transforming growth factor beta (TGF- β) signaling (2,3) and smooth muscle cells apoptosis, degrading the support of the aorta (4). Aneurysm formation is the result. Indeed, the leading cause of premature death in MFS patients is aortic dissection after progressive dilatation due to the local increased aortic wall stiffness (5). Accordingly, clinical management aims for prevention of aortic dissection by regular evaluation of local aortic diameter and screening for abnormal luminal growth in combination with β -blocker treatment to slow down aortic growth (6-8). However, many MFS patients even when treated, develop eventually aortic dilatation and even dissection. Furthermore, aortic dissection may also occur in non-dilated aortas (6). Therefore, investigation of other risk factors, such as aortic stiffness, is recommended for predicting progressive aortic dilatation (9-11).

A marker of aortic stiffness is the aortic pulse wave velocity (PWV), defined as the propagation speed of the systolic velocity wave front through the aorta. PWV-assessment by magnetic resonance imaging (MRI) is a well-validated method to non-invasively quantify arterial stiffness (12). Recently, an improved MRI-technique with two-directional in-plane velocity-encoding (VE) covering the whole aorta in a multi-slice volume scan has been introduced for the assessment of regional and local PWV (13). This approach results in dense PWV-sampling at 200 points along the aorta centerline, thereby enabling global, regional and local PWV-assessment (13). It is expected that in MFS patients, with local variability of disease manifestation, PWV-assessment with in-plane VE MRI potentially allows for the detection of subtle changes in local aortic stiffness and thereby the identification of areas at risk. To our knowledge, the predictive value of regional aortic stiffness described by PWV, for luminal aortic growth in MFS patients has not been reported before.

The purpose of the current study was therefore to investigate whether increased regional PWV at baseline (increased with respect to age-related normal values) can predict regional aortic luminal growth at 2-year follow-up in patients with MFS.

METHODS

Patient population and protocol

Twenty-one MFS patients and 26 healthy volunteers (without history of cardiac diseases) were prospectively studied with MRI in our institution. Written informed consent was obtained from each subject and the study protocol conformed to the Declaration of Helsinki and was approved by the Medical Ethical Committee. MFS patients were eligible for inclusion when 1) the diagnosis of MFS has been established according to the Ghent criteria (14), 2) they had no history of aortic surgery and 3) significant aortic valve or

mitral valve insufficiency was excluded by echocardiography. Patients were diagnosed with MFS in specialized outpatient clinics in the Netherlands (Leiden University Medical Center, Leiden, the Netherlands (n=18); Amsterdam University Medical Center, Amsterdam, the Netherlands (n=3)). Patients temporarily refrained from beta-adrenergic blocking medication and were at least 24 hours without this medication prior to MRI.

All patients underwent baseline and follow-up MRI examination (median follow-up: 24 months (25-75%: 23-25 months)) to assess both regional aortic stiffness (PWV), by using velocity-encoded MRI and regional aortic lumen area, by using contrast-enhanced magnetic resonance angiography (MRA). In addition, twenty-six healthy volunteers were included to acquire age-related normal PWV-values. Of note, the healthy volunteers underwent only the baseline velocity-encoded (VE) MRI examination to acquire age-related normal PWV values and they did not undergo MRA examination.

For patients, first the regional PWV were compared against these age-related normal values and were considered to be increased if PWV exceeded age-related normal values by 2 standard errors of the regression coefficients. Second, the incidence of regional luminal growth in the MFS patients, between baseline and follow-up MRI was assessed. Consecutively, the predictive value of PWV at baseline for regional luminal growth at follow-up was analyzed.

MRI acquisition

MRI was performed with a 1.5T scanner (Philips Intera, release 11 and 12; Philips Medical Systems, Best, the Netherlands; pulsar gradient system with amplitude 33 mT/m, 100mT/m/ms slew rate, and 0.33 ms rise time). Imaging sequences were previously described (13). In short, after acquisition of a series of thoracic survey images which were used for planning purposes, a three-slice volume slab (covering a double-oblique sagittal view of the aorta) was obtained with a steady-state free precession (SSFP) sequence and used for planning the VE MRI acquisitions (13).

Pulse wave velocity

PWV was assessed by means of two consecutive multi-slice two-directional in-plane VE MRI acquisitions of the three-slice double-oblique sagittal volume slab of the aorta. Velocity-encoding was performed in phase-encoding (i.e., anterior-posterior (AP)) direction and in frequency-encoding (i.e., feet-head (FH)) direction consecutively. The velocity-sensitivity was set to 150 cm/s. The body coil was used for signal reception. Scan parameters encompassed 60% rectangular field-of-view FOV 450x270 mm², 10mm slice thickness, echo time TE 2.4ms, repetition time TR 4.3ms, flip angle α 10°, acquisition voxel size 3.5x2.1x10.0mm³, sampling bandwidth 495 Hz and number of signal averages NSA 2. Retrospective gating was performed with maximal number of phases reconstructed. The true temporal resolution (TRes) amounted to 8.6ms (equals 2xTR). Acquisition was performed with free breathing and mean scan time of a single acquisition amounted to 7 minutes 8 seconds at a typical heart rate of 65 bpm.

Contrast-enhanced magnetic resonance angiography

In addition, contrast-enhanced magnetic resonance angiography (CE-MRA) of the full aorta was performed by first-pass imaging of a 25mL contrast bolus Dotarem (Guerbet, Gorinchem, the Netherlands) with a molarity of 0.5mmol/mL. Contrast was intravenously injected in the basilic, brachial or cephalic vein at an infusion rate of 2mL/s, and subsequently flushed by 20mL saline at 2mL/s, using Spectris Powerinjector (Medrad, Warrendale, USA). Contrast arrival time for the CE-MRA acquisition (i.e. the appropriate scan delay time after contrast injection) was obtained by imaging a transection of the proximal descending aorta continuously for one minute during injection of a 2 mL timing bolus, which was injected with the same infusion rate and saline flush. The contrast arrival time was determined by using region of interest analysis of the aortic lumen, to produce a time-intensity curve and obtain the *time-to-peak* arterial contrast enhancement. Consecutively the CE-MRA of the full aorta was performed with 3D T1-weighted fast gradient-echo sequence (85% rectangular FOV 500 x 80 mm², 50 slices of 1.6mm slice thickness, TE 4.6ms, TR 1.3ms, α 40°, acquisition voxel size 1.25x2.46x3.20 mm³, sampling bandwidth 238Hz and NSA 1). Breath-holding at end-expiration was performed.

Image analysis

Regional PWV and aortic luminal area were obtained from MRI data. MRI analysis of MFS patients with respect to the patient characteristics was performed blinded. A schematic representation of image acquisition and analysis in a MFS patient is provided in Figure 1. The aorta was divided into five segments (Figure 1A); the ascending aorta (S1), which included the aortic root, the tubular portion of the ascending aorta and extending to the brachiocephalic artery origin; the aortic arch (S2), which begins at the origin of the brachiocephalic artery, extending to the left common subclavian artery; the thoracic descending aorta (S3) which begins at the left common subclavian artery extending to the level of the diaphragm; the suprarenal abdominal aorta (S4) from the level of the diaphragm to the origin of the renal arteries; the infrarenal abdominal aorta (S5). The aortic segments for CE-MRA (at both baseline and follow-up) and PWV-analysis (at baseline) were registered manually by registration of the aortic centerline that was calculated during PWV- and CE-MRA image processing. Only after this image analysis was completed, results for PWV and CE-MRA analyses were combined.

Regional pulse wave velocity

Regional PWV was obtained from the two-directional, three-slice in-plane velocity-encoded MRI data using in-house developed MASS software, as described (13) (Figure 1D). The aorta was segmented in all three double-oblique sagittal views and the aortic centerline was automatically defined from this segmentation. Perpendicular to this centerline, at 200 sampling positions along the aorta, equidistant lines were automatically placed. Along each of these lines, the velocity was sampled and the maximal velocity per line was recorded, resulting in the maximal velocity wave form (constructed from the velocity components in AP and FH direction in each phase of the cardiac cycle) of blood

flowing along the aortic centerline. Wave propagation analysis was performed to determine the pulse wave arrival at each sampling position automatically, by foot detection of the wave. The diastolic flow velocity was modeled as a horizontal line and the upslope of the wave front was modeled by linear regression of 20% to 80% of all values along the slope. The pulse wave arrival time was then determined by the intersection of both lines. Regional PWV per segment was obtained from the relation between pulse wave arrival time versus sampling location along the aortic centerline. This relation was determined by linear regression. PWV was then defined by the inverse of the slope of this linear relation between pulse wave arrival time and the sampling position. This regional PWV was obtained for each of the five aortic segments (Figure 1E).

Normal values of regional PWV per segment were determined from the healthy volunteer data. The age-relation of these normal values was determined by linear regression ($PWV = A \times \text{Age} + B$). Consecutively, regional PWV of the MFS patients were compared

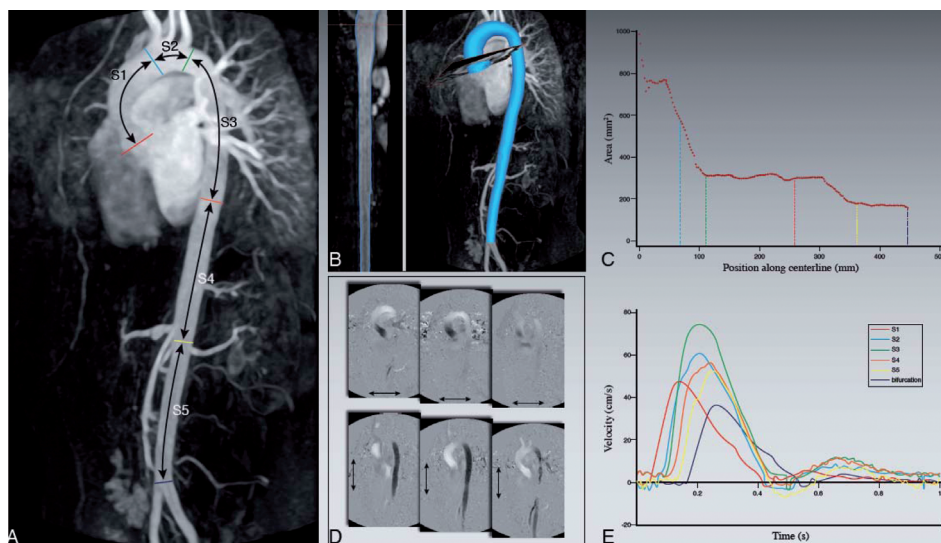


Figure 1. Representation of image acquisition and analysis in a MFS patient. Regional aortic luminal area and regional PWV were obtained from MRI data. **Figure 1A.** Maximum-intensity-projection of contrast-enhanced (CE) MRA data of an MFS patient. Five aortic segments were evaluated: ascending aorta (S1), aortic arch (S2), thoracic descending aorta (S3) suprarenal abdominal aorta (S4) and infrarenal abdominal aorta (S5). **Figure 1B.** The CE-MRA image analysis was performed using in-house developed LAVA software with automated centerline detection and 3D deformable modeling. **Figure 1C.** From CE-MRA data, cross-sectional luminal area was determined at 200 equidistantly-spaced sample points along the aortic centerline. For both baseline and 2-year follow-up, the mean lumen area per segment was determined. **Figure 1D.** PWV was obtained from two-directional, three-slice in-plane velocity-encoded MRI data using in-house developed MASS software, by calculating the relation between pulse wave arrival time at 200 equidistantly-spaced sample points along the aortic centerline and the position of these sample points along the centerline (**Figure 1E**). The centerline of PWV analysis was registered manually to the MRA centerline, and MRA centerline at baseline and follow-up were also manually registered. Regional PWV was determined for each of the five aortic segments.

against these age-related normal values. The PWV assessed in MFS was considered increased if this value exceeded the predicted normal PWV (predicted according to the age of the patient) with two standard errors for each of the regression coefficients. Accordingly, PWV is increased if $PWV > ((A + 2 \times SE_A) \times AGE + (B + 2 \times SE_B))$.

Aortic luminal growth

From CE-MRA data in patients, the mean cross-sectional luminal area per aortic segment was determined at baseline and at 2-year follow-up (Figure 1B.). Image analysis was performed using in-house developed and validated LAVA software with automated 3D centerline detection and automated segmentation using deformable tube modeling (15). The required user-interaction for centerline detection and lumen segmentation was limited to the placement of start and end point in the 3D data. Automated lumen segmentation resulted in a tube fit of the aorta. Next, the cross-sectional luminal area was determined at 200 equidistantly-spaced positions along the centerline (Figure 1C.). When required, the lumen segmentation was corrected manually on the cross-sectional view of the aorta. Image analysis resulted in a mean luminal area per segment. Assuming a circular shape, the mean diameter was calculated for each segment, both for baseline and follow-up.

A mean aortic luminal diameter increase from baseline to follow-up (2 years) of more than 2mm was considered significant growth. This cut-off represents a substantial increase, based on typical MFS aortic growth characteristics (16) and a comparable definition (mean aortic diameter increase > 1mm/year) has been used previously (10).

Intra- and inter-observer analysis

Intra- and inter-observer analysis for repeated image analysis was performed. Five patients were selected at random; one observer performed image analysis twice (with inter-examination time more than 6 months) and another observer repeated the analysis, blinded to the results of the other observer. For each patient, baseline MRA and PWV-analysis was repeated. Regional aortic lumen area and PWV were obtained, for aortic segments 2 to 5 (segment 1 was not taken into account, as for this segment, no anatomical start point marker was defined), resulting in a total of 20 evaluable measurements.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD). Parameters describing blood pressure (BP) and PWV were compared between MFS patients and healthy volunteers using unpaired t-tests. For the healthy volunteers, linear regression analysis was performed ($PWV = A \times Age + B$) in each of the five aortic segments. Age-related normal values were defined from this data for each segment, with PWV within limits of 2 standard errors of the regression coefficients. In MFS patients, the incidence of increased PWV per aorta segment was calculated as well as the incidence of aortic luminal growth over 2-year follow-up. In addition, sensitivity, specificity, positive and negative predictive value of regional PWV-assessment for predicting aorta luminal growth were calculated. Statistical analysis was performed using SPSS v 18.0 (SPSS Inc., Chicago, IL).

RESULTS

Twenty-one MFS patients (mean age: 36 years (min-max: 18-63 years)), diagnosed according to the Ghent criteria, were evaluated (14). Patient characteristics at the time of inclusion are summarized in Table 1. Eleven patients (52%) were male and all patients were adults at time of inclusion. Marfan genetic mutations were found in 18 patients (86%). Pathologic mutations in the fibrillin-1 gene were identified in 17 patients (81%), whereas in 1 patient (5%) a pathologic mutation in transforming-growth factor-2 receptor was found. A positive family history for MFS was found in 17 (81%) of the patients. Fourteen (66%) of the patients were on β -blocker medication.

In addition, the clinical characteristics of the twenty-six healthy volunteers (mean age: 30 years (min-max: 15-58 years)), are also provided in Table 1. Gender, mean age, blood pressure, heart rate and BMI were not significantly different between patients and volunteers. Patients with MFS were generally taller compared to the healthy volunteers, which was also evident from the larger body surface area.

Table 1. Characteristics of MFS patients

Characteristics	MFS Patients (n=21)	Healthy volunteers (n=26)	p-value
Demographics			
Male/female	11 (52%) /10 (48%)	16 (62%) /10 (39%)	0.5
Age at baseline MRI (years)	36 $\pm$ 15	30 $\pm$ 10	0.12
Brachial blood pressure (mmHg)			
Systolic	124 $\pm$ 11	122 $\pm$ 15	0.6
Diastolic	73 $\pm$ 9	71 $\pm$ 11	0.5
Heart rate (beats/minute)	66 $\pm$ 10	67 $\pm$ 10	0.95
Height (cm)	187 $\pm$ 10	177 $\pm$ 10	0.003
Body surface area (m ²)	2.11 $\pm$ 0.27	1.9 $\pm$ 0.2	0.005
Body mass index (kg/ m ²)	25 $\pm$ 5	23 $\pm$ 3	0.2
Ectopia Lentis	8 (38%)		
Mitral valve prolapse	9 (43%)		
Aortic root diameter by MRI (mm)	40.0 $\pm$ 3.4		
Genetic mutation	18 (86%)		
Fibrillin-1	17 (81%)		
Transforming growth factor-2 receptor	1 (5%)		
β -blocker use	14 (66%)		
ACE inhibitors	5 (24%)		

Data are presented as number (percentage) or as mean $\pm$ standard deviation. Abbreviations: MFS: Marfan syndrome; MRI: magnetic resonance imaging; ACE: Angiotensin converting enzyme.

Pulse wave velocity

Mean regional PWV-values for MFS patients and volunteers are presented in Table 2.

In twenty-six healthy volunteers, regional PWV was determined for five aortic segments. Of note, in three volunteers, the most distal segment S5 (infrarenal aorta) was not included in the PWV acquisition volume due to elongation of the aorta.

In twenty-one MFS patients, a total of 102 aortic segments was evaluated. In three patients, S5 was not included in the PWV acquisition volume due to elongation of the aorta. Mean regional PWV was significantly increased in patients with Marfan syndrome as compared to the healthy volunteers in similar age range, in all aortic segments. However, although the mean value of PWV in the ascending aorta (segment 1) was higher for MFS patients as compared to healthy volunteers, these values were not statistically significantly different, due to the wide standard deviation.

Age-related normal PWV values were acquired from the results of the linear regression analyses for the relation between age and regional PWV in the healthy volunteer cohort (Table 3). Regional PWV values significantly correlated with age (Pearson R between 0.39 and 0.57), except for segment 2 (aortic arch) and segment 5 (infrarenal abdominal aorta). In MFS patients, regional PWV at baseline was increased when compared with age-related normal values in 17 segments (17%) of 13 MFS patients.

Table 2. Comparison of mean PWV per aortic segment between MFS patients and healthy volunteers

Aortic Segment	MFS patients (n=21)	Healthy Volunteers (n=26)	p-value
PWV S1 (m/s)	6.1 ± 3.5	5.4 ± 1.2	0.3
PWV S2 (m/s)	5.9 ± 3.3	4.2 ± 1.9	0.03
PWV S3 (m/s)	6.3 ± 2.9	4.9 ± 1.1	0.02
PWV S4 (m/s)	6.3 ± 2.1	5.1 ± 1.1	0.01
PWV S5 (m/s)	7.4 ± 3.3	5.1 ± 1.6	0.007

Data are presented as mean ± standard deviation.

Abbreviations: MFS: Marfan syndrome; PWV: Pulse Wave Velocity; S1: ascending aorta; S2: aortic arch; S3: thoracic descending aorta; S4: suprarenal abdominal aorta; S5: infrarenal abdominal aorta.

Table 3. Linear regression analysis PWV in healthy volunteers per aortic segment: $PWV = A \times \text{Age} + B$

Aortic Segment	A ± SE	B ± SE	Pearson R
PWV S1 (m/s)	0.05 ± 0.02	3.76 ± 0.66	0.46 (p=0.017)
PWV S2 (m/s)	-0.02 ± 0.04	4.63 ± 1.19	-0.09 (p=0.672)
PWV S3 (m/s)	0.06 ± 0.02	3.12 ± 0.55	0.57 (p=0.003)
PWV S4 (m/s)	0.06 ± 0.02	3.39 ± 0.55	0.55 (p=0.004)
PWV S5 (m/s)	0.06 ± 0.03	3.39 ± 0.95	0.39 (p=0.067)

Data are presented as mean ± standard error (SE).

Abbreviations: PWV: Pulse Wave Velocity; SE: standard error; S1: ascending aorta; S2: aortic arch; S3: thoracic descending aorta; S4: suprarenal abdominal aorta; S5: infrarenal abdominal aorta.

Cross-sectional luminal area of the aorta

In the MFS patients, a mean aorta trajectory of 44±4cm was evaluated. For all MFS patients, mean aortic diameter measurements for baseline and follow-up per aortic segment are provided in Table 4. Significant luminal growth at follow-up was reported in 14 out of 102 aortic segments (14%) and in 7 (33%) of the MFS patients.

Table 4. Aortic Diameter measurements in MFS Patients for baseline and follow-up.

Aortic Segment	Baseline	Follow-up	p-value
Diameter S1 (mm)	27.1 ± 2.8	27.7 ± 3.1	0.14
Diameter S2 (mm)	22.3 ± 2.5	23.4 ± 2.9	0.002
Diameter S3 (mm)	20.4 ± 2.4	20.8 ± 2.4	0.001
Diameter S4 (mm)	18.7 ± 2.3	19.1 ± 2.1	0.028
Diameter S5 (mm)	14.9 ± 1.3	15.0 ± 1.3	0.161

Data are presented as mean ± standard deviation.
Abbreviations: MFS: Marfan syndrome; S1: ascending aorta; S2: aortic arch; S3: thoracic descending aorta; S4: suprarenal abdominal aorta; S5: infrarenal abdominal aorta.

Prediction of aortic luminal growth with PWV

The incidence of increased PWV per aortic segment is presented in Table 5. For the ascending aorta (segment 1), PWV was increased in five MFS patients, for the aortic arch (segment 2) in four MFS patients, for the thoracic descending aorta (segment 3) in three MFS patients, for the suprarenal abdominal aorta (segment 4) in two patients and for the infrarenal abdominal aorta (segment 5), three patients showed increased baseline PWV. The incidence of luminal increase per aortic segment is presented in Table 5. Significant luminal growth was present in three MFS patients for segment 1, in six patients for segment 2 and in 1 patient for segment 4. In the other segments (S3 and S5), no significant

Table 5. Diagnostic performance of regional PWV-testing for prediction of luminal aortic growth at 2-year follow up in MFS patients.

Aortic Segment	Incidence of Increased PWV	Incidence of Luminal Increase	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Aorta S1	5 (24%)	3 (14%)	33% (2-88%)	78% (52-93%)	20% (1-70%)	88% (60-98%)
Aorta S2	4 (19%)	6 (29%)	17% (1-64%)	80% (51-95%)	25% (1-78%)	71% (44-89%)
Aorta S3	3 (14%)	0 (0%)	NA	86% (63-96%)	NA	100% (78%-100%)
Aorta S4	2 (10%)	1 (5%)	0% (0%-90%)	90% (67%-98%)	0% (0-80%)	95% (72%-99%)
Aorta S5	3 (17%)	0 (0%)	NA	83% (58%-96%)	NA	100% (75%-100%)

Abbreviations: MFS: Marfan syndrome; S1: ascending aorta; S2: aortic arch; S3: thoracic descending aorta; S4: suprarenal abdominal aorta; S5: infrarenal abdominal aorta; NA: not applicable.

luminal increase was observed. Of note, two patients (S1: n=1; S2: n=1) presented with both increased PWV at baseline and luminal increase at follow-up.

Furthermore, the sensitivity, specificity and positive and negative predictive value for PWV predicting regional luminal growth are presented in Table 5. Specificity of regional PWV-testing in patients with Marfan syndrome was $\geq 78\%$ for all aortic segments. For segments 3 and 5, sensitivity and positive predictive value are not provided, since for those segments, none of the MFS patients presented an increased aortic luminal area at follow-up.

Intra- and inter-observer analysis

Results for intra- and inter-observer analysis for repeated image analysis are presented in Table 6. Intra-class correlation showed excellent agreement for intra- and inter-observer analysis for both PWV analysis as well as MRA-assessment for cross-sectional luminal area. The variation for PWV-assessment amounted to 12% and 9% for the MRA-assessment.

Table 6. Intra- and inter-observer analysis for both PWV analysis as MRA-assessment for cross-sectional luminal area

	Intra-observer		Inter-observer	
	PWV	MRA	PWV	MRA
Intra-class correlation	0.90 ($p < 0.001$)	0.96 ($p < 0.001$)	0.96 ($p < 0.001$)	0.99 ($p < 0.001$)
Mean difference $\pm$ SD	0.09 ± 0.64 (m/s)	3 ± 25 mm ²	0.12 ± 0.70 m/s	-3 ± 9 mm ²
95% CI (m/s)	$-0.2 - 0.4$ m/s	$-8 - 14$ mm ²	$-0.2 - 0.4$ m/s	$-7 - 1$ mm ²
p-value t-test	0.54	0.59	0.46	0.22
Coefficient of variation	12%	9%	13%	3%

Abbreviations: PWV: Pulse Wave Velocity; MRA: magnetic resonance angiography; 95% CI: 95% confidence interval.

DISCUSSION

In the present study, the diagnostic performance of regional PWV-sampling with velocity-encoded MRI for prediction of aortic luminal growth in MFS patients was evaluated. The main findings of this study are: (i) regional PWV was increased in MFS patients as compared to healthy volunteers in similar age range, in all aortic segments; (ii) regional PWV-assessment has moderate to high specificity for predicting absence of regional aortic luminal growth in MFS patients, as $\geq 78\%$ of the cases of without regional aortic luminal growth at 2-year follow-up presented without increased regional PWV at baseline. Of note, regional PWV-assessment lacks sensitivity, since only $\leq 33\%$ of the cases with aortic luminal growth presented with increased regional PWV at baseline.

In patients with MFS, aortic stiffness assessment can potentially provide complementary prognostic value to the monitoring of the aortic diameter for disease progression. In our study, regional aortic stiffness at five aortic segments was expressed by PWV-

assessment from in-plane velocity-encoded MRI. When compared to age-related normal values, the regional PWV at baseline was increased in 17% of all studied aortic segments of these selected MFS patients. Furthermore, significant luminal growth at follow-up was reported in 14% of the aortic segments. Of note, the diagnostic performance of regional PWV-testing for prediction of regional aortic luminal growth at 2-year follow-up showed moderate to high specificity for all aortic segments.

To our knowledge, the predictive value of regional aortic stiffness, described by PWV for luminal aortic growth in MFS patients, has not been reported before. In a previous study by Nollen et al. in 78 non-operated MFS patients, the predictive value of aortic stiffness both *locally* by distensibility assessment at a single position and *regionally* by PWV-assessment from through-plane velocity-encoded MRI was investigated for patients with progressive aortic dilatation (10). Aortic stiffness, calculated at a *local* level by distensibility was an independent predictor of progressive descending thoracic aortic dilatation. However, in the same study, the authors reported that PWV from through-plane VE MRI did not hold predictive value for aortic luminal growth in the descending thoracic aorta. This fact may possibly be explained by the limited accuracy due to the low temporal resolution (i.e. 25ms) of the MRI-sequence that was used by Nollen et al. A temporal resolution of 25ms is low considering the transit-time between flow waves at ascending and proximal descending aorta is in the order of 20ms. In comparison, we used a temporal resolution of 8.6ms. Furthermore, they used the half-peak of the flow wave as definition of pulse wave arrival, whereas in our study the foot of the velocity wave was used, a definition that should be more robust when automated transit-time assessment is less corrupted by early wave reflections and not affected by distal damping of the wave front (17).

A previous study showed that regional PWV-assessment from in-plane VE MRI with high temporal resolution (i.e. 8.6ms) shows higher agreement with invasive pressure measurements, the true gold standard for PWV-assessment (13), than PWV-assessment from through-plane VE MRI. Furthermore, regional aortic stiffness assessment with in-plane VE MRI at 200 sampling positions along the aorta centerline may be more sensitive in detecting regional stiffness variation. Of note, performing multiple local aortic stiffness assessment by distensibility calculations from maximal and minimal cross-sectional lumen area at 200 positions over the total aortic length is impracticable with respect of the extensive MRI planning and elaborate post-processing, and the local pulse pressure, which is required for distensibility calculations, may only be accurately assessed invasively. On the other hand, local PWV-assessment from in-plane VE MRI is feasible in terms of scan duration and post-processing time.

Groenink et al. showed that PWV from through-plane VE MRI was increased in MFS patients as compared to a control group with corresponding mean age for both the entire aorta and PWV in three segments of the aorta (ascending aorta-aortic arch, thoracic descending aorta and abdominal descending aorta) (6). Similar to that study, we found that PWV was increased in MFS patients as compared to healthy volunteers in all aortic segments. However, for the ascending aorta (segment 1) the difference in mean

PWV between MFS patients and volunteers was not statistically significant. This finding may be explained by the fact that MFS patients in this study cohort can be considered as relatively healthy (i.e., well regulated by medical treatment) since aortic surgery was not indicated yet for these patients at the time of study and MFS has a variable manifestation of disease. In addition, MRI in the ascending aorta is prone to respiratory blurring and movement of the aorta during the cardiac cycle, more than in other parts of the aorta. This might have reduced accuracy in this part of the aorta, both for MRA as well as PWV-assessment.

In adult MFS patients, current guidelines for prophylactic replacement of aortic root include excessive aortic growth, defined as growth of the aortic diameter of ≥ 5 mm/year (6,18). In our study, we used the definition of significant luminal increase of >2 mm diameter growth at 2-year follow-up. Using this definition, 10 (14%) of the evaluated aortic segments showed significant luminal increase. In total, 7 patients (33%) presented with significant luminal growth in at least one aortic segment.

Some MFS patients experience acute dissections even in the presence of non- or moderately-dilated aortas (6). Therefore, next to applying the current clinical guidelines, also monitoring of the entire aortic diameter with respect to other risk factors for aortic dissection, such as aortic stiffness, may prove to hold predictive value for disease progression (10,11,19). In our study, at least 78% of the cases without regional aortic luminal growth at follow-up presented without increased regional PWV at baseline. Therefore, regional PWV-assessment by VE MRI has moderate to high specificity for all aortic segments in these MFS patients. This finding implies that regional PWV-assessment is good at demonstrating absence of progressive disease. In contrast, 33% or less of the cases which presented with increased regional PWV at baseline revealed regional aortic luminal growth at follow-up. This finding implies that regional PWV-assessment lack sensitivity as it seems marginal at detecting present disease. Consequently, the risk-stratification strategy presented (i.e., regional PWV-testing) can be used to rule out progressive disease, which potentially is very useful for managing patients. Therefore, regional PWV-testing may potentially be useful complimentary to other clinical parameters, i.e. aortic diameter assessment.

A potential limitation of our study is the selection of a relatively healthy population of MFS patients (which had not yet undergone elective aortic surgery at the time of study) and the short follow-up duration. By evaluating these selective patients during a longer follow-up duration, more patients might reveal progressive aortic dilatation. Typically studies show differences between healthy volunteers and *very abnormal*s. The *near normal*s (relatively healthy MFS patients) described in the present study represent a tougher cohort where imaging can be really of benefit. However, we need to acknowledge that our present findings are based on a relatively small study population and need to be validated in a larger and more challenging study population. Furthermore, since the healthy volunteers did not undergo a CE-MRA acquisition and no follow-up MRI examination, analysis between MFS patients and healthy volunteers was not performed blinded. However, analysis of MFS patients with respect to the patient characteristics

was blinded. In addition, aortic segments for the PWV-analysis and the CE-MRA analysis were co-registered by the aortic centerline. Only after this image analysis was completed, results for PWV and CE-MRA analyses were combined. Of note, MRA aortic centerline detection is semi-automated (15). Importantly, for PWV analysis, the arrival time of each of the 200 wave forms was automatically determined as previously described (13). Of note, accuracy of regional PWV-assessment may depend on the segment length, since including a longer trajectory with more sampling points may result in more accurate weighting of the pulse wave transit-time over this particular segment. In addition, the curvature of the proximal aorta and the motion during the cardiac cycle that the proximal aorta is subjected to as compared to the more distal aorta is potentially an additional source of error, as well as the presence of branches that may lead to early wave reflections that can corrupt the automated definition of the foot of the pulse wave.

Conclusion

Regional PWV was significantly increased in selected MFS patients as compared to healthy volunteers within similar age range, in all aortic segments except in the ascending aorta. Furthermore, regional PWV-assessment has moderate to high specificity in MFS patients, as $\geq 78\%$ of the cases without regional aortic luminal growth at 2-year follow-up presented without increased regional PWV at baseline.

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REFERENCES

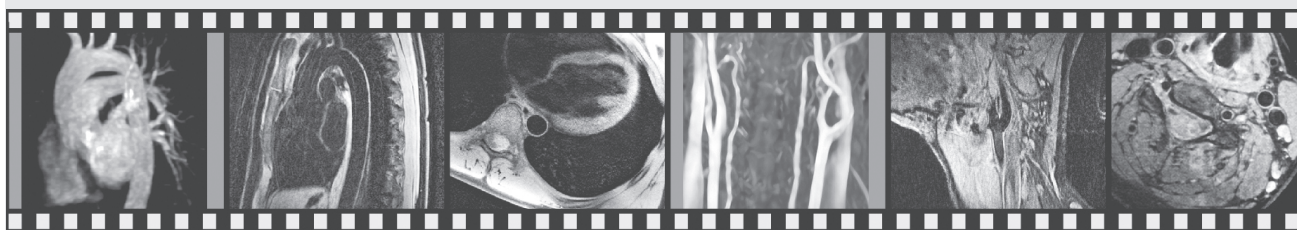
1. Dietz HC, Cutting GR, Pyeritz RE et al. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Nature* 1991;352:337-339.
2. Habashi JP, Judge DP, Holm TM et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science* 2006;312:117-121.
3. Radonic T, de WP, Baars MJ, Zwinderman AH, Mulder BJ, Groenink M. Losartan therapy in adults with Marfan syndrome: study protocol of the multi-center randomized controlled COMPARE trial. *Trials* 2010;11:3.
4. Yetman AT, Graham T. The dilated aorta in patients with congenital cardiac defects. *J Am Coll Cardiol* 2009;53:461-467.
5. Murdoch JL, Walker BA, Halpern BL, Kuzma JW, McKusick VA. Life expectancy and causes of death in the Marfan syndrome. *N Engl J Med* 1972;286:804-808.
6. Groenink M, Lohuis TA, Tijssen JG et al. Survival and complication free survival in Marfan's syndrome: implications of current guidelines. *Heart* 1999;82:499-504.
7. Milewicz DM, Dietz HC, Miller DC. Treatment of aortic disease in patients with Marfan syndrome. *Circulation* 2005;111:e150-e157.
8. Pyeritz RE, Loeys B. The 8th International Research Symposium on the Marfan Syndrome and related conditions. *Am J Med Genet A* 2011.
9. Hirata K, Triposkiadis F, Sparks E, Bowen J, Wooley CF, Boudoulas H. The Marfan syndrome: abnormal aortic elastic properties. *J Am Coll Cardiol* 1991;18:57-63.
10. Nollen GJ, Groenink M, Tijssen JG, van der Wall EE, Mulder BJ. Aortic stiffness and diameter predict progressive aortic dilatation in patients with Marfan syndrome. *Eur Heart J* 2004;25:1146-1152.
11. Elefteriades JA, Farkas EA. Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. *J Am Coll Cardiol* 2010;55:841-857.
12. Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness current understanding and future directions. *J Am Coll Cardiol* 2011;57:1511-1522.
13. Westenberg JJ, de Roos A, Grotenhuis HB et al. Improved aortic pulse wave velocity assessment from multislice two-directional in-plane velocity-encoded magnetic resonance imaging. *J Magn Reson Imaging* 2010;32:1086-1094.
14. de Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet* 1996;62:417-426.
15. de Koning PJ, Schaap JA, Janssen JP, Westenberg JJ, van der Geest RJ, Reiber JH. Automated segmentation and analysis of vascular structures in magnetic resonance angiographic images. *Magn Reson Med* 2003;50:1189-1198.
16. Meijboom LJ, Timmermans J, Zwinderman AH, Engelfriet PM, Mulder BJ. Aortic root growth in men and women with the Marfan's syndrome. *Am J Cardiol* 2005;96:1441-1444.
17. Stevanov M, Baruthio J, Gounot D, Grucker D. In vitro validation of MR measurements of arterial pulse-wave velocity in the presence of reflected waves. *J Magn Reson Imaging* 2001;14:120-127.
18. Legget ME, Unger TA, O'Sullivan CK et al. Aortic root complications in Marfan's syndrome: identification of a lower risk group. *Heart* 1996;75:389-395.
19. Hirata K, Kawakami M, O'Rourke MF. Pulse wave analysis and pulse wave velocity: a review of blood pressure interpretation 100 years after Korotkov. *Circ J* 2006;70:1231-1239.
20. Coats AJ, Shewan LG. Statement on authorship and publishing ethics in the international journal of cardiology. *Int J Cardiol* 2011;153:239-240.

CHAPTER 6

COUPLING BETWEEN MRI-ASSESSED REGIONAL AORTIC PULSE WAVE VELOCITY AND LUMINAL DIAMETERS IN PATIENTS WITH THORACIC AORTIC ANEURYSM – A FEASIBILITY STUDY

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ABSTRACT

Purpose: Thoracic aortic aneurysm (TAA) is potentially life-threatening and requires close follow-up to prevent aortic dissection. Aortic stiffness and size are considered to be coupled. Regional aortic stiffness in patients with TAA is unknown. We aimed to evaluate coupling between regional pulse wave velocity (PWV), marker of vascular stiffness, and aortic diameter in TAA patients.

Methods: In 40 TAA patients (59 ± 13 years, 28 male), regional aortic diameters and regional PWV were assessed by 1.5T MRI. The incidence of increased diameter and PWV were determined for five aortic-segments (S1, ascending-aorta; S2, aortic-arch; S3, thoracic-descending-aorta; S4, suprarenal and S5, infrarenal abdominal-aorta). In addition, coupling between regional PWV testing and aortic dilatation was evaluated and specificity and sensitivity were assessed.

Results: Aortic diameter was 44 ± 5 mm for the aortic root and 39 ± 5 mm for the ascending aorta. PWV was increased in 36 (19%) aortic segments. Aortic diameter was increased in 28 (14%) segments. Specificity of regional PWV-testing for prediction of increased regional diameter was $\geq 84\%$ in the descending thoracic to abdominal aorta and $\geq 68\%$ in the ascending aorta and aortic arch.

Conclusion: Normal regional PWV is related to absence of increased diameter, with high specificity in the descending-thoracic to abdominal-aorta and moderate results in the ascending-aorta and aortic-arch.

INTRODUCTION

Thoracic aortic aneurysm (TAA) is a life-threatening disease which requires close follow-up to intervene before aortic dissection and/or rupture occurs. The incidence of aortic disease increases and has been estimated at 10.4 cases per 100 000 person/years (1,2). A TAA grows asymptotically and slowly, at approximately 0.1 to 0.42 cm per year (3-5). Besides increase of aortic diameter, mechanical properties of the aneurismal aorta deteriorate (6). Assessment of mechanical properties of the aorta (i.e. aortic stiffness) may be useful to supplement symptoms and size as criteria for prophylactic aortic intervention (7).

Aortic pulse wave velocity, a well-validated surrogate marker of arterial stiffness, is defined as the propagation speed of the systolic velocity wave front through the aorta (8). PWV-assessment by magnetic resonance imaging (MRI), using velocity-encoding (VE) allows for a full three-dimensional visualization of the aorta, thereby permitting reproducible positioning of imaging planes along the aorta (9). Moreover, MRI allows for the assessment of global, regional and local PWV at different locations of the arterial tree (8). PWV-assessment from VE-MRI, when compared directly to PWV-assessment from invasive pressure measurements (the gold standard), had excellent correlation and reproducibility (8,10).

In patients with Marfan Syndrome (MFS), increased global and regional aortic wall stiffness has been reported (11). Furthermore, PWV in the aortic arch showed statistically significant more increase with age, suggesting more pronounced aortic involvement in the proximal aorta (11). This is also a possible risk factor for aortic dissection and therefore regional PWV assessment can be of clinical value in patients with TAA. It is expected that in TAA patients *without* MFS, local aortic wall stiffness measured by PWV is increased. Interestingly, regional aortic wall stiffness and size are considered to be coupled (6,12). However, the local aortic wall stiffness, measured by PWV in TAA patients, has not been reported before. Therefore, the purpose of the present study was 1) to investigate the local aortic wall stiffness measured by PWV in TAA patients and 2) to evaluate coupling between regional PWV and aortic diameter and 3) to assess sensitivity and specificity for the coupling between regional PWV testing and aortic dilatation in TAA patients.

METHODS

Patient population and study protocol

The study population consisted of forty adult TAA patients. Selection criteria were: 1) age between 18-80 years, 2) asymptomatic for aortic dilatation and/or dissection and 3) regularly clinically evaluated at the outpatient clinic, including MRI examination of the entire aorta. Exclusion criteria were: 1) MFS and related disorders (left out by clinical

evaluation and/or DNA analysis) and 2) history of aortic surgery, significant aortic valve or mitral valve regurgitation.

All patients underwent a comprehensive MRI examination to assess both regional aortic lumen diameter and regional aortic stiffness (PWV), by using VE MRI. Patients temporarily refrained from beta-adrenergic blocking medication and were at least 24 hours without this medication prior to MRI.

First, the regional aortic maximal diameter and regional PWV were compared against age-related normal values and the incidence of increased aortic diameter and/or increased segmental PWV was determined. Second, sensitivity and specificity for the coupling between regional PWV testing and aortic dilatation in TAA patients were assessed. The study was conducted with the approval of Leiden University Medical Center Institutional Review Board with specific waiver of the need for individual patient consent.

MRI Acquisition

MRI acquisition was performed with a 1.5T scanner (Philips Intera, release 12; Philips Medical Systems, Best, the Netherlands; pulsar gradient system with amplitude 33 mT/m, 100mT/m/ms slew rate, and 0.33 ms rise time).

Acquisition of aortic dimensions

Aortic dimensions were assessed from the acquisition of conventional 1] cine bright-blood gradient-echo imaging in coronal (Figure 1 A) and sagittal (Figure 1 B) direction and 2] 2D black-blood spin-echo imaging (Figure 1 C). To visualize the entire aorta, a three-dimensional, T1-weighted fast gradient-echo sequence was used to obtain a contrast-enhanced magnetic resonance angiography (CE-MRA) of the full aorta, as previously described (Figure 1D) (12).

Acquisition of aortic PWV

Regional PWV was assessed by two consecutive three-slice two-directional in-plane VE MRI acquisitions as described before (12). Velocity-encoding was performed in phase-encoding (i.e., anterior-posterior) direction and in frequency-encoding (i.e., feet-head) direction consecutively. The velocity-sensitivity was set to 150 cm/s and we used scan parameters as described earlier (12). In short, 60% rectangular field-of-view FOV 450x270 mm², 10mm slice thickness, echo time TE 2.4ms, repetition time TR 4.3ms, flip angle α 10°, acquisition voxel size 3.5x2.1x10.0mm³, sampling bandwidth 495 Hz and number of signal averages NSA 2. Retrospective gating was performed with maximal number of phases reconstructed. The true temporal resolution amounted to 8.6ms (equals 2xTR). Acquisition was performed with free breathing. Mean scan time of a single acquisition was 7 minutes and 8 seconds, at a typical heart rate of 65 beats/ minute.

Image analysis

A schematic representation of image acquisition and analysis for aortic diameter and aortic PWV in a TAA patient is provided in Figure 1 and 2 respectively. The aorta was

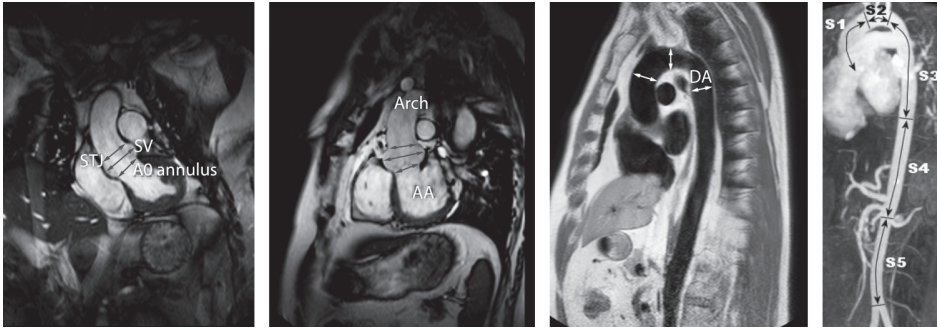


Figure 1. Representation of image acquisition and analysis of aortic dimensions in a TAA patient.

Figure 1A and **B** are acquired by conventional cine bright blood gradient-echo imaging. **Figure 1A** is taken in the oblique sagittal plane and **Figure 1B** in the oblique coronal plane. **Figure 1A and B** show the levels of the aortic annulus (Ao annulus), sinuses of valsalva (SV) and sino-tubular junction (STJ) where maximal luminal diameters were evaluated. **Figure 1C** is acquired by 2D black blood spin-echo imaging and shows the levels of the ascending aorta (AA), aortic arch (Arch) and thoracic descending aorta (DA) where maximal aortic diameters were measured. **Figure 1D** is a maximum intensity projection of a contrast-enhanced magnetic resonance angiogram, acquired by first-pass imaging with a three-dimensional, T1-weighted fast gradient-echo sequence, representing the entire aorta.

For both analysis of aortic dimensions and for analysis of aortic PWV, five aortic segments were evaluated: the ascending aorta (S1), the aortic arch (S2), the thoracic descending aorta (S3), the suprarenal abdominal aorta (S4), the infrarenal abdominal aorta (S5).

Abbreviations: Ao = aorta; SV = sinuses of valsalva; STJ = sino-tubular junction; AA = ascending aorta; DA = descending aorta.

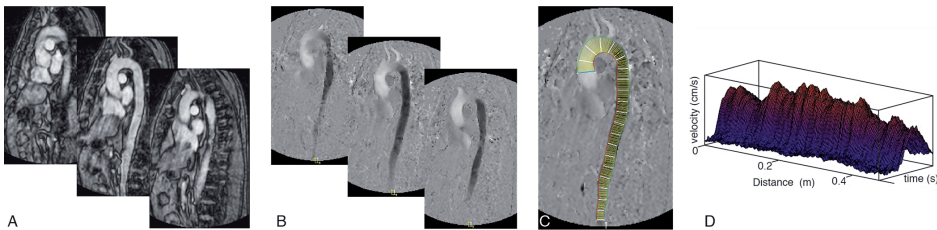


Figure 2. Representation of image acquisition and analysis of regional PWV in a TAA patient.

Regional PWV was assessed by means of combining two consecutive acquisitions of a stack of three consecutive slices (**Figure 2A**), both with one-directional velocity-encoding in anterior-posterior and feet-head direction (**Figure 2B**), respectively. The stack of three slices covered the entire aorta.

Using MASS MRI software, 200 equidistantly-spaced sampling chords were defined (**Figure 2C**).

At each sampling chord, the maximal velocity along the aortic centerline was determined for each cardiac phase, resulting in 200 velocity-time waveforms (**Figure 2D**). From the corresponding measurement position (distance (x)) along the aortic centerline and time of arrival of the pulse wave (arrival time (t)) at each position, the local aortic pulse wave velocity was determined.

Abbreviations: PWV = pulse wave velocity; TAA = thoracic aortic aneurysm; VE = velocity-encoded; MRI = magnetic resonance imaging.

divided into five segments; the ascending aorta (S1), which included the aortic root, the tubular portion of the ascending aorta and extending to the brachiocephalic artery origin; the aortic arch (S2), which begins at the origin of the brachiocephalic artery, extending to the left subclavian artery; the thoracic descending aorta (S3) which begins at the left subclavian artery extending to the level of the diaphragm; the suprarenal abdominal aorta (S4) from the level of the diaphragm to the origin of the renal arteries; the infrarenal abdominal aorta (S5) (Figure 1).

Analysis of aortic dimensions

Maximal diameters were evaluated on the conventional cine gradient echo and spin-echo images at the level of the aortic annulus, aortic root, sino-tubular junction, the thoracic ascending aorta, the aortic arch, and the thoracic descending aorta. An example is provided in Figure 1 A-D. The aortic dimensions in TAA patients were considered increased if the values exceeded the criteria as described in the guidelines for the diagnosis and management of patients with thoracic aortic segments (13). In detail, for the aortic root, aortic enlargement was quantified based on age- and body size-adjusted Roman criteria (13,14). For segment 1, the age- and body size adjusted Hannuksela criteria were used (13,15), for segment 2, a cut off of 30mm was used, based on the guidelines (13), for segment 3, again, the age- and body size adjusted Hannuksela criteria were used (13,15). And for segment 4 and 5, aortic dilatation was diagnosed when the aorta exceeds a generally agreed to standard diameter or when a given aortic segment was larger than contiguous aortic segments of apparently normal size, according to the guidelines (13).

Mean diameter per aortic segment was obtained from the CE-MRA data, using in-house developed and validated software for automated vessel analysis (LAVA software) [15].

Analysis of aortic PWV

Regional PWV was obtained from the VE MRI data, using in-house developed MASS software. (10). An example is provided in Figure 2A-D. After manual segmentation of the aorta, the aortic centerline was automatically determined and 200 equidistantly-spaced sampling chords were defined. For each chord and each phase the maximal velocity wave form was determined, resulting in 200 maximal velocity waveforms (10,12,16). The arrival time (time (t)) of each of the 200 waveforms at their corresponding positions (distance (x)) along the aortic centerline was automatically determined and PWV, defined as $\Delta x / \Delta t$, was calculated (10,12,16). This regional PWV was obtained for each of the five aortic segments.

Consecutively, regional PWV values from the TAA patients were compared with age-related normal values (using linear regression: $PWV = A \times Age + B$) from a healthy volunteer cohort (12). The PWV was considered increased if this value exceeded the predicted normal PWV with two standard errors (SE) for each of the regression coefficients ($PWV > ((A + 2 \times SE_A) \times AGE + (B + 2 \times SE_B))$).

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD). Sensitivity and specificity were calculated for the coupling between regional aortic pulse wave velocity assessment and regional aortic dilatation in TAA patients. Statistical analysis was performed using SPSS v 20.0 (SPSS Inc., Chicago, IL).

RESULTS

Forty patients (59 ± 13 years) were evaluated. Patient characteristics at the time of inclusion are summarized in Table 1. Twenty-eight patients (70%) were male. Patients were often hypertensive or used antihypertensive medication ($n=27$, 68%).

Aortic diameter

Maximal aortic diameter was 27 ± 3 mm for the aortic annulus; 44 ± 5 mm for the aortic root and 36 ± 5 mm for the sino-tubular junction.

For the aortic segments, mean and maximal aortic diameter dimensions are provided in Table 2.

PWV values

Mean regional PWV-values are presented in Table 2. A total of 194 aortic segments were evaluated. Of note, 6 aortic segments (S1; $n=1$, S2; $n=3$; S5; $n=2$) were considered failed (3%), potentially due to excessive patient movement, and therefore not included in the analysis.

Coupling between PWV and aortic diameters

The incidence of increased aortic dimensions and the incidence of increased PWV are presented in Table 3. Regional PWV was increased in 36 (19%) aortic segments (S1: 8 cases, S2: 11 cases, S3: 7 cases, S4: 6 cases, S5: 4 cases). In total, 18 (45%) TAA patients presented with increased regional PWV in ≥ 1 aortic segment. The aortic root was increased in 38 (95%) out of the 40 TAA patients. For the five aortic segments distal to the aortic root, in 21 (53%) out of the 40 patients regional aortic diameter was increased in at least one aortic segment. Regional aortic diameter was increased in a total of 28 (14%) segments (S1: 15 cases, S2: 6 cases, S3: 4 cases, S4: 2 cases, S5: 1 cases) (Table 3). Table 3 shows that the incidence of increased regional diameter was lower in the more distal aortic segments versus the more proximal aortic segments.

Table 3 shows incidence of increased PWV and diameter and the sensitivity and specificity for the coupling between PWV and diameter. Specificity was $\geq 84\%$ in the descending thoracic to abdominal aorta and $\geq 66\%$ in the ascending aorta and aortic arch.

Normal regional PWV demonstrated absence of increased diameter, with high specificity in the descending thoracic to abdominal aorta and moderate results in the ascending aorta and aortic arch.

Of note, in general regional PWV-assessment lacked sensitivity with low to marginal results for all aortic segments.

Table 1. Demographic and clinical characteristics of TAA patients (n=40)

Demographics		
Male/female		28 (70%) / 12 (30%)
Age at MRI (years)		59 ± 13
Clinical characteristics		
Height (cm)		180 ± 10
Body mass index (kg/m ²)		27 ± 4
Body surface area (m ²)		2.1 ± 0.2
Brachial blood pressure (mmHg)		
Systolic		134 ± 20
Diastolic		79 ± 11
Heart rate (beats/minute)		66 ± 10
MRI assessed left ventricular dimensions and function		
EDV (ml)		164 ± 38
EDV/BSA (ml/m2)		80 ± 19
ESV (ml)		69 ± 23
ESV/BSA (ml/m2)		34 ± 12
EF (%)		62 ± 5
Cardiovascular risk factors		
Hypertension*		27 (68%)
Current Smoker		7 (18%)
Hypercholesterolemia†		16 (40%)
Diabetes mellitus		1 (3%)
Obesity‡		7 (18%)
Previous myocardial infarction		4 (10%)
Cardiovascular medication		
β-blocker		17 (58%)
ACE-inhibitor		21 (53%)
Anticoagulants		16 (40%)
Statins		13 (33%)

Data are presented as number (percentage) or as mean ± standard deviation.

Abbreviations: EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction; BSA, body surface area.

*Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mmHg or use of antihypertensive medication.

†‡Serum total cholesterol ≥230 mg/dl or serum triglycerides ≥200 mg/dl or treatment with lipid-lowering drugs

‡Body mass index ≥30 kg/m²

Table 2. Aortic dimensions and PWV per aortic segment (n=40)

Aortic segment	Diameters (<i>maximal</i> luminal diameter, mm)	Diameters (<i>mean</i> luminal diameter, mm)	PWV (m/s)	PWV, Number of patients analyzed
S1: Ascending aorta	39.4 ± 5.3	34.8 ± 4.2	7.7 ± 4.8	39
S2: Aortic arch	28.7 ± 3.2	29.4 ± 2.7	7.7 ± 5.6	37
S3: Thoracic descending aorta	26.6 ± 5.7	24.3 ± 2.7	8.5 ± 3.9	40
S4: Suprarenal abdominal aorta	25 ± 3	22.4 ± 2.6	8.3 ± 4.0	40
S5: Infrarenal abdominal aorta	18.5 ± 3.2	17.2 ± 3.7	8.3 ± 4.0	38

Data are presented as mean ± standard deviation.

Abbreviations: PWV: pulse wave velocity; S1: ascending aorta; S2: aortic arch; thoracic descending aorta; S4: suprarenal abdominal aorta; S5: infrarenal abdominal aorta.

Table 3. Diagnostic performance (i.e. sensitivity and specificity) of regional PWV-testing in predicting regional aortic dilatation.

N	Aortic Segment	Incidence of increased		Sensitivity (CI)	Specificity (CI)	Positive Predictive Value (CI)	Negative Predictive Value (CI)
		PWV	diameter				
39	S1: Ascending aorta	8 (21%)	15 (38%)	13% (2-42%)	75% (53-89%)	25% (4-64%)	58% (39-75)
37	S2: Aortic arch	11 (28%)	6 (16%)	17% (1-64%)	68% (49-83%)	9% (0-43)	81% (60-93)
40	S3: Thoracic descending aorta	7 (18%)	4 (10%)	75% (22-99%)	89% (73-96%)	43% (12-80%)	97% (82-100%)
40	S4: Suprarenal abdominal aorta	6 (15%)	2 (5%)	0% (0-80%)	84% (68-93%)	0% (0-48%)	94% (79-99%)
38	S5: Infrarenal abdominal aorta	4 (10%)	1 (3%)	100% (5-100%)	92% (77-98%)	25% (1-78%)	100% (87-100%)

Data are presented as number (percentage).

Abbreviations: N, number of patients analyzed; CI, 95% confidence interval, PWV: pulse wave velocity; S1: ascending aorta; S2: aortic arch; S3: thoracic descending aorta; S4: suprarenal abdominal aorta; S5: infrarenal abdominal aorta.

DISCUSSION

The main finding of the study is that normal regional PWV is related to absence of increased diameter in patients with TAA, with high specificity in the descending thoracic to abdominal aorta and moderate results in the ascending aorta and aortic arch.

Formation of TAA is influenced by the interaction of genetic and environmental factors resulting in aortic media degeneration and breakdown of elastic fibers leading to aortic

dilatation and affecting aortic elasticity (13,17-19). The investigation of the mechanical properties of the aorta (i.e. aortic stiffness) may be useful to supplement symptoms and size as criteria for prophylactic aortic intervention (7).

Previously, aortic stiffness, measured by PWV was an independent predictor of progressive aortic dilatation in patients with MFS. PWV assessment from through-plane VE MRI is widely used and allows for PWV calculation between two locations at a certain distance along the aorta (20,21). However, changes of mechanical properties of the aorta are typically regional. Accordingly, in the present study *regional* aortic stiffness from in-plane VE MRI was densely sampled at 200 positions along the aortic centreline. When compared to age-related normal values, the regional PWV was increased in 36 (19%) of all studied aortic segments of these selected TAA patients. Furthermore, increased regional aortic diameter was reported in 28 (14%) of the aortic segments.

Regional aortic wall stiffness and size are considered to be coupled (6,12). We previously showed that regional PWV had moderate to high specificity for predicting absence of regional aortic luminal growth in MFS patients (12). To our knowledge, the incidence of increased regional aortic stiffness, as described by PWV and the coupling between aortic stiffness and regional aortic dilatation in TAA patients without MFS, has not been reported before. In the present study, we observed that in TAA patients, regional PWV-testing is associated with high specificity ($\geq 84\%$) for regional aortic dilatation in the descending thoracic to abdominal aorta and provided moderate results (specificity $\geq 66\%$) in the ascending aorta and aortic arch. These findings imply that regional PWV-assessment in TAA patients can be used to demonstrate absence of present disease (i.e. increased aortic diameter). In contrast, regional PWV-testing showed low sensitivity, in particular in the ascending aorta and aortic arch, although aortic dilatation is frequently present in these segments. These findings implicate that regional PWV-testing is marginal at detecting present disease.

We also observed increased aortic stiffness in the more distal aortic segments, suggesting that aortic wall abnormalities extend into the entire aorta.

At present, the implication of PWV-assessment for patient management remains unclear (8). The current study suggests that aortic stiffness is coupled to aortic diameter. Confirming normal PWV values at follow-up may rule out aortic media disease including aortic stiffening and aortic dilatation. On the other hand, increased PWV in an otherwise non-dilated aortic segment may suggest impaired aortic condition and present aortic media disease, accordingly careful monitoring and treatment is then required. Ultimately, assessment of regional aortic stiffness may even demonstrate regions of the aneurysm at high risk of disruption (7). These issues, however, are still unclear. Accordingly, our center will prospectively follow and monitor both the structural and mechanical parameters of this cohort to provide more evidence and direction for the clinical use of regional PWV-assessment in TAA patients.

Limitations

The following limitations need to be acknowledged. Our findings are based on a relatively small and healthy TAA study population (which had not yet undergone elective aortic surgery). Since the incidence of aortic dilatation of especially the abdominal aorta was low in the present study population, sensitivity and specificity values cannot be translated to all TAA patients. Our findings need to be validated in a larger study population and also in patients with more extensive disease progression. Furthermore, the age range of TAA patients extended beyond the age range of the healthy volunteer data used for obtaining age-related normal values (12). We performed an extrapolation by linear regression to calculate age-related normal values of PWV for cases with higher age, using the same relation as used within the age range of healthy volunteers. PWV was considered increased, when exceeding the predicted normal PWV (predicted according to the age of the patient) with two standard errors for each of the regression coefficients ($PWV > ((A + 2 \times SE_A) \times AGE + (B + 2 \times SE_B))$).

Next, accuracy of regional PWV-assessment may depend on the segment length. We divided the aorta into five standard anatomical segments, with a relative short segment 2 (i.e. aortic arch). A longer trajectory with more sampling points may potentially result in more accurate PWV assessment. Additional sources of error for the proximal aorta are the aorta curvature, the presence of branches leading to early wave reflections thereby potentially corrupting the automated definition of the foot of the pulse wave and the motion during the cardiac cycle. Additionally, in the proximal part of the aorta, breathing motion may all have effect of the accuracy of PWV-assessment. These limitations may partly explain the moderate results in the ascending aorta and aortic arch, as compared to the (thoracic) descending aorta. However, the currently used technique for dense PWV-sampling with in-plane VE MRI at 200 sampling positions, allows for global, regional and local PWV-assessment with high temporal resolution (i.e. 8.6 ms), which is much higher than the temporal resolution of the through-plane VE MRI technique currently used for PWV assessment in literature (10). Therefore, potentially our technique allows for detection of more subtle changes in local aortic stiffness.

Conclusion

In TAA patients, normal regional PWV demonstrated absence of increased diameter, with high specificity in the descending thoracic to abdominal aorta and moderate results in the ascending aorta and aortic arch.

1 REFERENCES

- 2 1. Clouse WD, Hallett JW, Jr., Schaff HV et al. Acute aortic dissection: population-based incidence
3 compared with degenerative aortic aneurysm rupture. *Mayo Clin Proc* 2004;79:176-180.
- 4 2. Clouse WD, Hallett JW, Jr., Schaff HV, Gayari MM, Ilstrup DM, Melton LJ, III. Improved prognosis of
5 thoracic aortic aneurysms: a population-based study. *JAMA* 1998;280:1926-1929.
- 6 3. Cambria RA, Gloviczki P, Stanson AW et al. Outcome and expansion rate of 57 thoracoabdominal
7 aortic aneurysms managed nonoperatively. *Am J Surg* 1995;170:213-217.
- 8 4. Coady MA, Rizzo JA, Hammond GL et al. What is the appropriate size criterion for resection of
9 thoracic aortic aneurysms? *J Thorac Cardiovasc Surg* 1997;113:476-491.
- 10 5. Davies RR, Goldstein LJ, Coady MA et al. Yearly rupture or dissection rates for thoracic aortic
11 aneurysms: simple prediction based on size. *Ann Thorac Surg* 2002;73:17-27.
- 12 6. Koullias G, Modak R, Tranquilli M, Korkolis DP, Barash P, Elefteriades JA. Mechanical deterioration
13 underlies malignant behavior of aneurysmal human ascending aorta. *J Thorac Cardiovasc Surg*
14 2005;130:677-683.
- 15 7. Elefteriades JA, Farkas EA. Thoracic aortic aneurysm clinically pertinent controversies and uncer-
16 tainties. *J Am Coll Cardiol* 2010;55:841-857.
- 17 8. Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness current understanding and
18 future directions. *J Am Coll Cardiol* 2011;57:1511-1522.
- 19 9. van der Wall EE. Crown years for non-invasive cardiovascular imaging (Part III): 30 years cardiovas-
20 cular magnetic resonance. *Neth Heart J* 2013;21:263-265.
- 21 10. Westenberg JJ, de Roos A, Grotenhuis HB et al. Improved aortic pulse wave velocity assessment
22 from multislice two-directional in-plane velocity-encoded magnetic resonance imaging. *J Magn*
23 *Reson Imaging* 2010;32:1086-1094.
- 24 11. Westenberg JJ, Scholte AJ, Vaskova Z et al. Age-related and regional changes of aortic stiff-
25 ness in the marfan syndrome: Assessment with velocity-encoded MRI. *J Magn Reson Imaging*
26 2011;34:526-531.
- 27 12. Kroner ES, Scholte AJ, de Koning PJ et al. MRI-assessed regional pulse wave velocity for predicting
28 absence of regional aorta luminal growth in marfan syndrome. *Int J Cardiol* 2012.
- 29 13. Hiratzka LF, Bakris GL, Beckman JA et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM
30 Guidelines for the diagnosis and management of patients with thoracic aortic disease: Executive
31 summary: A report of the American College of Cardiology Foundation/American Heart Asso-
32 ciation Task Force on Practice Guidelines, American Association for Thoracic Surgery, American
33 College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists,
34 Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology,
35 Society of Thoracic Surgeons, and Society for Vascular Medicine. *Anesth Analg* 2010;111:279-315.
- 36 14. Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two-dimensional echocardiographic aortic
37 root dimensions in normal children and adults. *Am J Cardiol* 1989;64:507-512.
- 38 15. Hannuksela M, Lundqvist S, Carlberg B. Thoracic aorta—dilated or not? *Scand Cardiovasc J*
39 2006;40:175-178.
- 40 16. Kroner ES, van der Geest RJ, Scholte AJ et al. Evaluation of sampling density on the accuracy of
41 aortic pulse wave velocity from velocity-encoded MRI in patients with Marfan syndrome. *J Magn*
42 *Reson Imaging* 2012;36:1470-1476.
17. Yetman AT, Graham T. The dilated aorta in patients with congenital cardiac defects. *J Am Coll*
Cardiol 2009;53:461-467.

18. Grewal N, DeRuiter MC, Jongbloed MR et al. Normal and abnormal development of the aortic wall and valve: correlation with clinical entities. *Neth Heart J* 2014;22:363-369.
19. Franken R, Radonic T, den Hartog AW et al. The revised role of TGF-beta in aortic aneurysms in Marfan syndrome. *Neth Heart J* 2014.
20. Grotenhuis HB, Westenberg JJ, Steendijk P et al. Validation and reproducibility of aortic pulse wave velocity as assessed with velocity-encoded MRI. *J Magn Reson Imaging* 2009;30:521-526.
21. Nollen GJ, Groenink M, Tijssen JG, van der Wall EE, Mulder BJ. Aortic stiffness and diameter predict progressive aortic dilatation in patients with Marfan syndrome. *Eur Heart J* 2004;25:1146-1152.

CHAPTER 7

**PULSE WAVE VELOCITY AND FLOW IN THE CAROTID
ARTERY: EFFECTS OF AGEING**

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ABSTRACT

Purpose: This study aimed to explore differences in arterial stiffness of the aorta and carotid artery, assessed by pulse wave velocity (PWV), to evaluate the blood flow volume distribution towards the carotid circulation and to assess the effect of aging on the coupling between aortic and carotid PWV, using velocity-encoded MRI.

Methods: Sixteen adult younger volunteers (age<30 years) and sixteen older volunteers (age>45 years) underwent 3T MRI examination to assess aortic and carotid flow volumes and PWV, using the transit time method.

Results: Aortic versus carotid PWV-ratio was 1.2 for younger volunteers and 0.95 for older volunteers, demonstrating leveling of wall stiffness. Furthermore, flow volume per minute in the internal carotid artery was lower for older versus younger volunteers (mean volume 177 ± 42 ml/min/m² versus 147 ± 32 ml/min/m², $p=0.028$), whereas aorta and common carotid artery flow volumes were not different. Consequently, the fraction of blood flow volume towards the brain was smaller for older versus younger volunteers ($61\pm9\%$ versus $71\pm8\%$, $p=0.002$).

Conclusions: PWV-leveling between aorta and carotid artery at older age is associated with a reduction in blood flow volume towards the brain. Velocity-encoded MRI can be used to evaluate PWV and flow volume distribution in the aortic arch and the carotid circulation.

INTRODUCTION

Vessel wall elasticity varies along the arterial tree and plays a central role in cardiovascular physiology by dampening the systolic pressure wave (1). It potentially serves as a protective mechanism, preventing end-organs such as the brain to be exposed to excessive pulsatile energy. Recent studies have suggested that excessive pulsatile energy transmitted from the aorta to the brain might be a factor in the occurrence of cerebrovascular lesions (1-4). In young, healthy adults, a physiological abrupt change in arterial stiffness at the interface between the compliant aorta and the stiffer carotid arteries creates a reflection site for pulsatile energy (aortic pressure) and the systolic blood flow wave. This wave reflection limits the transmission of pulsatile energy into the carotid circulation (3).

Arterial wall stiffness is positively related with aging (5). It is hypothesized that with advancing age a marked increase in aortic stiffness in association with an attenuation of stiffening of the carotid artery reduces the stiffness mismatch at the interface (4). As a result, wave reflections at this interface may be reduced possibly leading to damaging end-organ effects on the arterioles in the brain (2,4).

Magnetic resonance imaging (MRI) is well-validated to study arterial wall stiffness. The aortic pulse wave velocity (PWV), defined as the propagation speed of the flow waveform or pressure pulse, is a clinically useful surrogate marker of aortic stiffness (6).

Velocity-encoded (VE) MRI is a well-validated technique to assess aortic PWV accurately and reproducibly (6-8). Since MRI is not hampered by the choice of imaging plane, this modality potentially enables wave propagation sampling along the carotid arterial trajectory from the common carotid artery into the internal carotid artery. However, the assessment of PWV of the carotid artery with VE MRI is challenging due to the need for high temporal resolution and adequate spatial resolution. Accordingly, there is only scarce literature describing carotid PWV-assessment with VE MRI. To our knowledge, only one conference proceeding described PWV measurements in the carotids in three healthy volunteers using Fourier velocity encoded MR (9). However, the Fourier velocity encoded MRI technique with high temporal resolution as described by Hardy et al. was developed as a research imaging tool that is not commercially available on all MRI platforms. Furthermore, no flow values can be assessed from these acquisitions.

The purpose of the current study was to use VE MRI to explore differences in arterial stiffness (i.e. by PWV-assessment) of the aorta and carotid artery, to evaluate the blood flow volume distribution towards the carotid circulation and to assess the effect of aging on the coupling between aortic and carotid PWV.

MATERIALS AND METHODS

Population and study protocol

Approval from the local medical ethics committee was obtained and all subjects gave written informed consent. Thirty-two healthy asymptomatic volunteers not associated with cardiovascular disease, stroke, transient ischemic attack (TIA) or dementia and without any medical treatment were included. The characteristics of the study population are summarized in Table 1. Mean heart rate was 62 ± 9 beats/minute and all volunteers had regular sinus rhythm. Fifteen volunteers (47%) were male. Mean BMI was 23.0 ± 2.2 kg/m².

The volunteers were divided into two age-groups: "younger adult volunteers" with age below 30 years (mean age of 25 ± 3 years) and "older volunteers" with age above 45 years (mean age of 56 ± 6 years). Body mass index (BMI) and body surface area (BSA) were not different between the two groups (Table 1). Subjects underwent 3T MRI examination (Philips Achieva Medical Systems, Best, The Netherlands) between August 2011 and March 2012 to assess PWV in the aortic arch and carotid artery.

Table 1. Characteristics of study population

	Total study population (n=32)	Younger volunteers age <30 years (n=16)	Older volunteers age >45 years (n=16)	p-value
Male/Female	15/17	7/9	8/8	
Age (years)	41 $\pm$ 16	25 $\pm$ 3 (range 20-29)	56 $\pm$ 6 (range 47-68)	
BMI (kg/m ²)	23 $\pm$ 2	22 $\pm$ 2	24 $\pm$ 2	0.07
BSA (m ²)	1.9 $\pm$ 0.2	1.8 $\pm$ 0.2	1.9 $\pm$ 0.2	0.31
Systolic blood pressure (mmHg)	124 $\pm$ 12	121 $\pm$ 9	127 $\pm$ 14	0.2
Diastolic blood pressure (mmHg)	75 $\pm$ 8	74 $\pm$ 7	77 $\pm$ 9	0.2
Heart rate (beats per minute)	62 $\pm$ 9	59 $\pm$ 9	65 $\pm$ 9	0.07

Data are represented as mean $\pm$ standard deviation.

Abbreviations: BMI: body mass index, BSA: body surface area.

MRI Acquisition

Aortic PWV (PWV_{aorta}) was assessed in the proximal part of the aorta only using a single acquisition plane transecting the ascending and proximal descending aorta as described before (2). Briefly, on a non-triggered thoracic survey scan with coronal and sagittal views a single one-directional through-plane velocity-encoded (VE) MRI-sequence was planned on a plane perpendicular to the ascending aorta, at the level of the pulmonary trunk, transecting both the ascending and proximal descending aorta (Figure 1 A1) to assess the blood flow velocity (Figure 1 A2). A dedicated cardiac coil (6-element phased-array coil) was used for signal reception. Scan parameters were: field-of-view

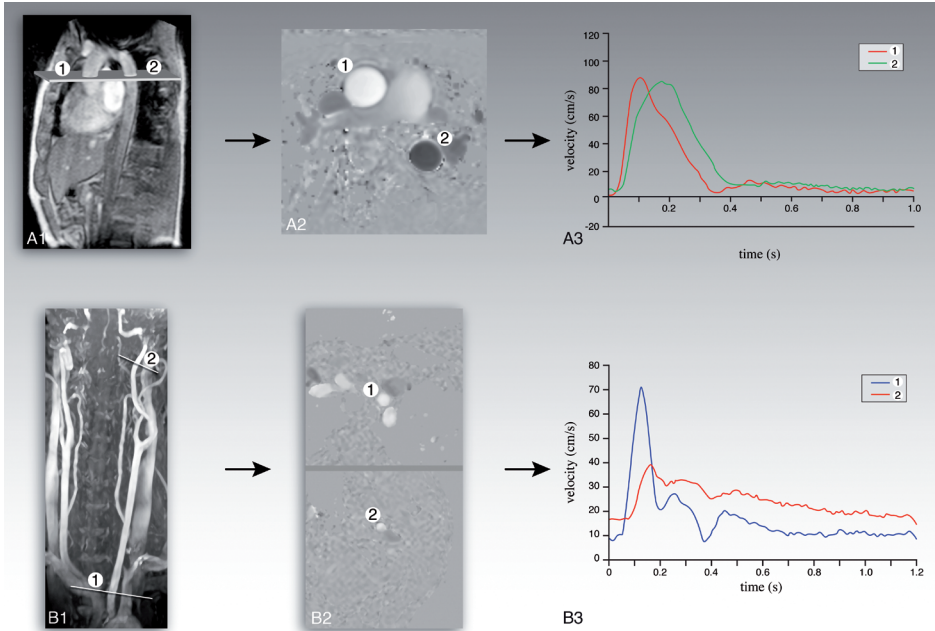


Figure 1. Pulse wave velocity assessment for both for the aortic arch and the carotid artery. **(A)** PWV_{aorta} was performed by one-slice through-plane velocity-encoded MRI at the level of the pulmonary trunk, transecting both the ascending aorta (1) and proximal descending aorta (2) (**A1**), with the corresponding velocity-encoded images (**A2**). From the propagation of the resulting velocity waveforms (**A3**), PWV_{aorta} is determined.

(B) $PWV_{carotid\ artery}$ was performed by two-slice through-plane velocity-encoded MRI at two locations, proximally at the left common carotid artery just above the aortic arch (1) and distally just below the petrous portion of the left internal carotid artery (2) (**B1**), which were planned on the maximum intensity projection of the carotid arteries, with the corresponding velocity-encoded images (**B2**). From the propagation of the resulting velocity waveforms (**B3**), $PWV_{carotid\ artery}$ is determined.

(FOV) $320 \times 260 \text{ mm}^2$, slice thickness 8 mm, flip angle (FA) 10° , repetition time (TR) 4.9 ms, echo time (TE) 2.9 ms, acquisition resolution $2.5 \times 2.5 \times 8.0 \text{ mm}^3$, number of signal averages (NSA) 1, velocity sensitivity (V_{enc}) 150 cm/s in through-plane direction. The true temporal resolution (TRes), defined as $2 \times TR$, amounted to 9.8 ms. Vector ECG-triggering with retrospective gating was used with maximal number of phases reconstructed. Scan duration depended on the subject's heart rate and was approximately 2 minutes at 60 beats per minute heart rate.

PWV in the carotid artery ($PWV_{carotid\ artery}$) was determined using a 16-element neuro-vascular head-neck coil, covering both the aortic arch as well as the carotid arteries up to the circle of Willis. First, a 3D time-of-flight (TOF) technique was used to visualize the full carotid trajectory for planning purposes of the subsequent VE MRI acquisitions. Scan parameters: T1-weighted gradient-echo, FOV $180 \times 172 \text{ mm}^2$, 350 over-contiguous slices, slice thickness 2 mm, TR 23 ms, TE 3.45 ms, FA 15° , acquisition resolution: $1.0 \times 2.8 \times 2.0$

mm³. PWV_{carotid artery} was assessed by two consecutive VE MRI acquisitions, planned using a rotational maximal-intensity-projection (MIP) of the TOF, perpendicular to the left carotid artery (Figure 1 B). The first acquisition was positioned proximally at the origin of the common carotid artery, just above the aortic arch and the second acquisition was positioned distal to the bifurcation and just below the petrous portion of the internal carotid artery (Figure 1 B1). Scan parameters were: FOV 200×200 mm², slice thickness 5mm, FA 10°, TR 6.2 ms, TE 3.4 ms, acquisition resolution 1.52×1.50×5.0 mm³, NSA 1, V_{enc} for first acquisition 150 cm/s and second acquisition 120 cm/s, both in through-plane direction. The true temporal resolution (TRes, defined as 2×TR, amounted to 12.4 ms). Vector ECG-triggering with retrospective gating was used with the maximal number of phases reconstructed. Scan duration depended on the subject's heart rate and was approximately 2 minutes for each acquisition.

Image analysis

PWV_{aorta} and PWV_{carotid artery} were both determined by the transit time method (10). The vascular path length (Δx), describing the distance between two sampling sites, i.e., at the ascending and the proximal descending aorta for PWV_{aorta} and at the origin of the carotid artery just above the aortic arch and at the internal carotid artery just below the petrous portion for PWV_{carotid artery}, was manually determined using MASS software (Leiden University Medical Center, Leiden, The Netherlands). For PWV_{aorta}, by manually placing a poly-line along the centerline of the aorta in the sagittal survey images and for PWV_{carotid artery} by placing a poly-line along the carotid centerline using the MIP of the TOF image. Wave propagation was evaluated from maximal velocity-time curves that were obtained at all sampling sites by using FLOW software (Leiden University Medical Center, Leiden, The Netherlands) with automated contour detection for image segmentation (Figure 1 A3). The foot-to-foot definition was used for Δt (i.e., the transit time) assessment; with automated detection of the foot of the systolic velocity wave front (i.e., the wave arrival time), by detection of the intersection point of a horizontal line modeling the constant diastolic flow and a line along upslope of the systolic wave front, modeled by linear regression along 20% to 80% of the range of the velocity values along this upslope. Accordingly, PWV was calculated as $\Delta x/\Delta t$ (m/s). By pixelwise integration of velocity, assessed in the ascending aorta, times the cross-sectional lumen area (i.e., the flow rate) per heart beat, times the number of heart beats per minute, the blood flow volume (in ml/min) was determined. Also for the carotid artery, the flow volume per minute (in ml/min) at both sampling sites (i.e., common carotid artery and internal carotid artery) was obtained by pixelwise integration. Both aortic and carotid flow volumes were indexed for body surface area (determined according to the Mosteller's formula) (11). The flow volume fraction (%) was calculated both for the flow volume from ascending aorta towards the common carotid artery as well as for the common carotid artery towards the internal carotid artery.

Image analysis was performed consecutively (non-blinded) after image acquisition. Only after image analysis was completed, the results for PWV analyses were combined.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD). The unpaired t-test was used to compare characteristics of the study population and MRI-derived properties of arterial wall stiffness and thickness. The paired t-test was used to compare aortic and carotid arterial stiffness within the same volunteers. In addition, mean differences ($\pm$ 95%-confidence intervals, 95%CI) were provided. Univariable linear regression analysis was performed to assess the association between age versus PWV for both younger and older volunteers, with age as a continuous variable. For comparing the age-relation between groups, the group classified as binary variable was included as an independent variable in the linear regression analyses. Regression lines and 95%CI of the slopes are reported.

RESULTS

Mean evaluated aortic arch trajectory was significantly longer for older volunteers versus younger volunteers: 132 ± 17 mm versus 99 ± 17 mm ($p < 0.001$). Mean evaluated carotid artery trajectory was not significantly different between both groups: 173 ± 12 mm versus 175 ± 11 mm ($p = 0.65$) for older versus younger volunteers, respectively.

Aortic and carotid PWV and stroke volumes

Mean values for PWV are presented in Table 2. When PWV was compared between both age-groups, both PWV_{aorta} and $PWV_{carotid\ artery}$ were significantly higher in the older volunteers when compared to the younger volunteers (PWV_{aorta} : 7.4 ± 1.4 m/s versus 4.9 ± 0.7 m/s, $p < 0.001$; $PWV_{carotid\ artery}$: 6.9 ± 1.5 m/s versus 5.7 ± 1.0 m/s, $p = 0.02$, both older

Table 2. PWV and flow of the aorta and carotid artery

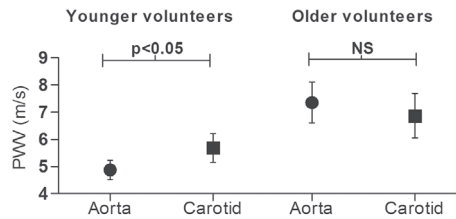
	Younger volunteers <i>age <30years</i> (n=16)	Older volunteers <i>age >45years</i> (n=16)	Mean difference (95%CI)	p-value
PWV aorta (m/s)	4.9 ± 0.7	7.4 ± 1.4	-2.5 (-1.7; -3.3)	<0.001
PWV carotid artery (m/s)	5.7 ± 1.0	6.9 ± 1.5	-1.2 (-2.1; -0.3)	0.015
PWV-ratio (PWV carotid artery:PWA aorta)	1.2 ± 0.2	0.95 ± 0.2	0.2 (0.07; 0.4)	0.003
Flow volume per minute / BSA (ml/min/m ²) Aorta	3012 ± 619	2860 ± 830	152 (-377; 680)	0.56
Common carotid artery	247 ± 49	241 ± 47	6 (-29; 41)	0.73
Internal carotid artery	177 ± 42	147 ± 32	30 (4; 57)	0.028
Fraction of flow volume (%) aorta : common carotid artery	8 ± 2	11 ± 10	-2 (-8; 3)	0.37
common carotid artery : internal carotid artery	71 ± 8	61 ± 9	10 (4; 16)	0.002

Data are represented as mean $\pm$ standard deviation. Mean difference is presented with 95% confidence interval.

Abbreviations: PWV: pulse wave velocity; 95%CI: 95% confidence interval; BSA body surface area.

1 versus younger volunteers) (Figure 2). Interestingly, while for the younger volunteers
 2 mean $PWV_{\text{carotid artery}}$ (5.7 ± 1.0 m/s) was significantly ($p=0.009$) higher as compared to
 3 mean PWV_{aorta} (4.9 ± 0.7 m/s), $PWV_{\text{carotid artery}}$ (6.9 ± 1.5 m/s) and PWV_{aorta} (7.4 ± 1.4 m/s) were
 4 not significantly ($p=0.26$) different for the older volunteers, indicating PWV-leveling
 5 between aorta and carotid artery at older age. This is also illustrated in Figure 2 and
 6 is evident when comparing PWV-ratios ($PWV_{\text{aorta}} / PWV_{\text{carotid artery}}$): 0.95 ± 0.2 for the older
 7 volunteers versus 1.2 ± 0.2 for the younger volunteers ($p=0.003$).

8 No significant differences between older and younger volunteers were observed in
 9 mean flow volume per minute, indexed for BSA, both for the ascending aorta as well as
 10 the common carotid artery. However, for the internal carotid artery, mean flow volume
 11 per minute, indexed for BSA, was significantly lower in the older volunteers as compared
 12 to the younger volunteers ($p=0.028$) (Table 2). Consequently, in older volunteers, a
 13 significantly lower fraction of flow volume towards the brain (flow volume from com-
 14 mon carotid artery towards internal carotid artery) was observed: $61 \pm 9\%$ versus $71 \pm 8\%$
 15 ($p=0.002$) for older versus younger volunteers, respectively.



25 **Figure 2.** Comparison of PWV_{aorta} and $PWV_{\text{carotid artery}}$ in younger volunteers (age <30 years, n=16) and older
 26 volunteers (age >45 years, n=16). Data are presented as mean $\pm$ confidence interval.

29 Associations between PWV and age

30 The results of linear regression analyses for the associations between age versus PWV
 31 in the aorta and carotid artery are presented in Figure 3, for both the younger and the
 32 older volunteers. In the younger volunteers, no association between age and PWV was
 33 found, neither for the aorta nor the carotid artery (Figure 3A). In contrast, in the older
 34 volunteers significant associations were found: an increase in PWV of 0.13 m/s (95% CI:
 35 0.013; 0.24) per incremental year for the aorta ($p=0.03$) and a slightly smaller increase
 36 of 0.09 m/s (95%CI: -0.04; 0.24) per incremental year for the carotid artery ($p=0.15$)
 37 (Figure 3B).

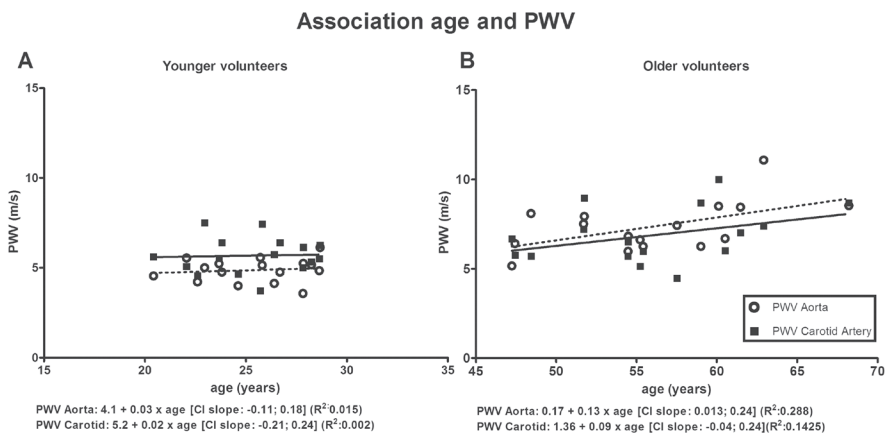


Figure 3. Associations between age and PWV in healthy volunteers. **3A.** Association between age and PWV in younger volunteers (age < 30 years). **3B.** Association between age and PWV in older volunteers (age < 45 years). Solid lines indicate the linear regression lines for PWVcarotid artery with age and dotted lines indicate the linear regression of PWVaorta with age.

DISCUSSION

To the best of our knowledge, this study is the first to report on pulse wave velocity assessment in both the aorta as well as the left carotid artery by using through-plane velocity-encoded MRI. The main findings of our study are: 1) older volunteers showed significantly higher aortic and carotid PWV as compared to younger volunteers, but the ratio between aortic and carotid PWV decreased to 0.95 indicating PWV-leveling at older age; 2) at older age, the flow volume per minute, indexed for BSA, towards the internal carotid artery and the relative flow volume from common towards internal carotid artery decreased.

Our findings highlight the potential of MRI for non-invasive assessment of regional PWV at multiple locations along the arterial tree. 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). In contrast, assessment of functional parameters such as arterial stiffness by PWV at different vascular territories for evaluating the predictive value for occurrence of vascular events is of clinical interest (6). Aortic stiffening is well-known to be associated with cardiovascular disease (6). The Rotterdam Study highlighted the predictive value of aortic PWV for occurrence of coronary artery disease and stroke, whereas carotid artery distensibility sampled by ultrasound had no additional predictive value (13). Recently, it was suggested by Mitchell et al., that the ratio between PWV_{aorta} and $PWV_{\text{carotid artery}}$ might be an independent predictor for specific end-organ damage in the brain, since a disproportionate increase in PWV_{aorta} with little

1 change in $PWV_{\text{carotid artery}}$ may facilitate transmission of excessive pulsatile energy towards
2 the brain microcirculation (3).

3 This study by Mitchell et al. revealed that in a community-based cohort (n=668),
4 stiffening of the aorta, as measured by echocardiography, was associated with reduced
5 wave reflection at the interface between carotid artery and aorta (3). A limitation of
6 their study was that the authors exclusively studied an older population. The observa-
7 tions from our small study sample are consistent with their findings although we also
8 included a younger population for evaluation of age effects. Moreover, our findings are
9 in line with literature in that the aorta stiffens with age, whereas age-related stiffening
10 of the carotid artery is more attenuated (1). Our data revealed in younger volunteers
11 a significant stiffer carotid artery when compared to the aortic arch, whereas in older
12 volunteers the difference between PWV_{aorta} and $PWV_{\text{carotid artery}}$ diminished, resulting in
13 PWV -leveling between the aorta and the carotid artery.

14 Previous studies almost exclusively used applanation tonometry and echo Doppler
15 for arterial stiffness assessment. Both modalities can only provide an estimation of the
16 global PWV due to the inability of accurate determination of the wave propagation path
17 length (7). Furthermore, only sampling in the common carotid artery is possible. Our
18 study showed that in older volunteers, age was a clear determinant of aortic stiffness
19 and to a lesser extent of carotid artery stiffness. This arterial-specific age-relation of
20 aortic and carotid arterial stiffness was evident from the larger increase in PWV_{aorta} with
21 age versus the attenuated increase in $PWV_{\text{carotid artery}}$. This finding is in line with a previous
22 study by Paini et al. in which univariate relationships between common carotid artery
23 stiffness and aortic stiffness determined by applanation tonometry were evaluated in
24 three different study populations, showing increased aortic stiffening versus carotid ar-
25 terial stiffening with age and other cardiovascular risk factors (14). Our findings revealed
26 an increase in PWV_{aorta} of 1.3 m/s per 10-year increase in age in the older volunteers
27 group, which is in line with the distribution of PWV -values according to age category in
28 a large European population (15).

29 Interestingly, the leveling of vascular stiffness between aorta and carotid artery
30 at older age was also associated with a higher reduction in flow towards the internal
31 carotid artery. When the wave reflection at the origin of the common carotid artery is di-
32 minished due to aging, the potential protective mechanism of limiting pulsatile energy
33 transmission towards the brain is lifted, which eventually resulted in a significant lower
34 fraction of flow volume towards the brain.

35
36 Our study has some limitations. First, it involves a cross-sectional design in a relatively
37 small population of healthy volunteers. Follow-up studies are needed to further elu-
38 cidate the associations between aortic and carotid PWV in normal volunteers and in
39 different patient populations. Second, since we aimed to evaluate the differences in
40 PWV -leveling and flow distribution between different age groups, we included only
41 volunteers of young (<30 years) and older age (>45years). Accordingly, no volunteers
42 between 30-45 years of age were included in our study.

Third, assessment of $PWV_{\text{carotid artery}}$ by VE MRI has not been validated against invasive pressure measurements as was previously done for PWV_{aorta} (7). However, the same imaging technique and image processing strategy were followed as for the well-validated PWV_{aorta} -assessment. In addition, for the assessment of $PWV_{\text{carotid artery}}$ the TRes amounted to 12.4 ms and the mean carotid artery trajectory length was 175 mm, therefore $PWV_{\text{carotid artery}}$ can be accurately assessed up to values of 14 m/s. In our study, $PWV_{\text{carotid artery}}$ ranged (min-max) from 3.7 to 10.0 m/s. For the aorta, PWV can accurately be assessed up to values of 12 m/s and in our study, PWV_{aorta} ranged (min-max) from 3.6 to 11.0 m/s. Increasing TRes even further, i.e. by using Fourier velocity encoded M-mode, an interleaved one-dimensional MRI technique (14,15), might be beneficial for the accuracy of PWV -assessment in the carotid artery, when elevated PWV are to be expected in patients (16).

Furthermore, only the through-plane velocity component was encoded for the assessment of the high-temporal velocity-time curves. Encoding velocity in all three directions is possible, and the penalty of scan time increment and reduction in TRes. Since the accuracy of PWV assessment based on the transit time method relies on high TRes and PWV assessment was the main objective in this study, only through-plane encoding was used. The acquisition planes were carefully planned perpendicular to the carotid artery segments, on two orthogonal views of the artery, in order to accurately obtain the volume flow through the common carotid artery as well as the internal carotid artery.

Conclusions

This is the first study to describe carotid artery pulse wave velocity assessment by using through-plane VE MRI. PWV and flow volume distribution in the aortic arch and the carotid circulation were evaluated. PWV -leveling between aorta and carotid artery at older age was associated with a reduction in blood flow volume towards the brain.

1 REFERENCES

- 2 1. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vascu-
- 3 lature: implications for end-organ damage. *J Appl Physiol* 2008;105:1652-1660.
- 4 2. Brandts A, van Elderen SG, Westenberg JJ et al. Association of aortic arch pulse wave velocity
- 5 with left ventricular mass and lacunar brain infarcts in hypertensive patients: assessment with MR
- 6 imaging. *Radiology* 2009;253:681-688.
- 7 3. Mitchell GF, van Buchem MA, Sigurdsson S et al. Arterial stiffness, pressure and flow pulsatility
- 8 and brain structure and function: the Age, Gene/Environment Susceptibility—Reykjavik study.
- 9 *Brain* 2011;134:3398-3407.
- 10 4. van Elderen SG, Brandts A, Westenberg JJ et al. Aortic stiffness is associated with cardiac func-
- 11 tion and cerebral small vessel disease in patients with type 1 diabetes mellitus: assessment by
- 12 magnetic resonance imaging. *Eur Radiol* 2010;20:1132-1138.
- 13 5. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease
- 14 enterprises: Part I: aging arteries: a “set up” for vascular disease. *Circulation* 2003;107:139-146.
- 15 6. Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness current understanding and
- 16 future directions. *J Am Coll Cardiol* 2011;57:1511-1522.
- 17 7. Grotenhuis HB, Westenberg JJ, Steendijk P et al. Validation and reproducibility of aortic pulse
- 18 wave velocity as assessed with velocity-encoded MRI. *J Magn Reson Imaging* 2009;30:521-526.
- 19 8. Kroner ES, van der Geest RJ, Scholte AJ et al. Evaluation of sampling density on the accuracy of
- 20 aortic pulse wave velocity from velocity-encoded MRI in patients with Marfan syndrome. *J Magn*
- 21 *Reson Imaging* 2012;36:1470-1476.
- 22 9. Hardy CJ, Marinelli L, Blezek D.J., Darrow R.D. MRI determination of pulse wave velocity in the
- 23 carotid arteries. *Proc.Intl.Soc.Mag.Reson.Med.* 16, 388. 2008.
- 24 10. Westenberg JJ, de Roos A, Grotenhuis HB et al. Improved aortic pulse wave velocity assessment
- 25 from multislice two-directional in-plane velocity-encoded magnetic resonance imaging. *J Magn*
- 26 *Reson Imaging* 2010;32:1086-1094.
- 27 11. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987;317:1098.
- 28 12. Den Ruijter HM, Peters SA, Anderson TJ et al. Common carotid intima-media thickness measure-
- 29 ments in cardiovascular risk prediction: a meta-analysis. *JAMA* 2012;308:796-803.
- 30 13. Mattace-Raso FU, van der Cammen TJ, Hofman A et al. Arterial stiffness and risk of coronary heart
- 31 disease and stroke: the Rotterdam Study. *Circulation* 2006;113:657-663.
- 32 14. Paini A, Boutouyrie P, Calvet D, Tropeano AI, Laloux B, Laurent S. Carotid and aortic stiffness:
- 33 determinants of discrepancies. *Hypertension* 2006;47:371-376.
- 34 15. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk
- 35 factors: ‘establishing normal and reference values’. *Eur Heart J* 2010;31:2338-2350.
- 36 16. Laurent S, Boutouyrie P. Arterial stiffness and stroke in hypertension: therapeutic implications for
- 37 stroke prevention. *CNS Drugs* 2005;19:1-11.
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PART III

IMAGING OF VESSEL WALL MORPHOLOGY AND FUNCTION

CHAPTER 8

COUPLING OF VESSEL WALL MORPHOLOGY AND FUNCTION IN THE AORTA AND THE CAROTID ARTERY: AN EVALUATION WITH MRI

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ABSTRACT

Purpose: To evaluate the regional association between vessel wall morphology (i.e. cross-sectional vessel wall area (VWA)) and function (i.e. wall stiffness expressed in the pulse wave velocity (PWV)) in both the aortic arch and the left carotid artery.

Methods: Thirty-two healthy volunteers (mean age 41 ± 16 years) underwent 3T MRI examination to assess PWV and VWA of the aorta and the left carotid artery. PWV was determined by the transit-time method with velocity-encoded MRI recordings of the systolic blood flow propagation. VWA was assessed for both the aorta and the carotid artery, by detecting lumen and outer vessel wall contours in cross-sectional black blood images. Linear regression analyses were used to test associations between aortic and carotid vessel wall area and stiffness.

Results: Within the same vascular territory, correlation between PWV and VWA was stronger than across vascular territories. For the aorta, the correlation between PWV_{AO} and VWA_{AO} ($r=0.71$, $p<0.0001$) was stronger than between PWV_{AO} and VWA_{CA} ($r=0.53$, $p=0.002$). For the carotid artery, the correlation between PWV_{CA} and VWA_{CA} ($r=0.61$, $p<0.0001$) was stronger than between PWV_{CA} and VWA_{AO} ($r=0.46$, $p=0.008$).

Conclusion: Morphologic and functional vessel wall properties assessed in the aortic arch and the left carotid artery are significantly stronger associated within the same vascular territory rather than across different vascular territories.

INTRODUCTION

Abnormal arterial stiffening and vessel wall thickening have proven to be associated with major cardiovascular disease end points, including heart disease and stroke (1). Therefore, arterial stiffness and cross-sectional vessel wall area (VWA) are commonly assessed to evaluate cardiovascular risk (2).

Aging interacting with various environmental factors exerts effect on both the morphology and function of the arterial vessel wall by media degeneration and breakdown of elastic fibers (3), eventually leading to an increased stiffness of the arterial vessel wall. Using echo Doppler, a different effect of age on arterial stiffening in the aortic arch as compared to the common carotid artery has been demonstrated (4).

In young healthy subjects, a portion of the systolic pressure waves is thought to be reflected due to the stiffness mismatch at the interface between the compliant aorta and the stiffer carotid arteries (5). Recently it was suggested that abnormal stiffening of the aorta may result in the loss of the protective effect of the stiffness mismatch, allowing excessive pulsatile energy transmitted from the aorta to the brain which might be a factor in the occurrence of cerebrovascular lesions (4,6).

Using magnetic resonance imaging (MRI) in combination with velocity-encoding (VE), non-invasive evaluation of both morphological (such as VWA) and functional vessel wall parameters (such as wall stiffness expressed in the pulse wave velocity (PWV)) is feasible in arbitrarily chosen vascular territories (1,7-10). PWV, defined as the propagation speed of the systolic pressure wave front through the aorta, is a proven and clinically useful surrogate marker of arterial stiffness (1). PWV assessment by MRI is a well-validated method to non-invasively quantify arterial stiffness (1,9,11). In contrast to echocardiography, MRI allows for a regional assessment of PWV, as MRI is not limited to the availability of suitable acoustic windows along the vascular tree.

We hypothesize that the association between PWV and VWA is regionally different between vascular beds and territories. Differential stiffening in various vascular territories may cause site-specific perfusion abnormalities supplying various organs such as the brain, the heart, the kidneys and alike. Accordingly, the purpose of this study was to assess the relationship between PWV and VWA in two vascular territories (i.e., the aortic arch and the left carotid artery, respectively) and across both territories.

MATERIAL AND METHODS

Population and study protocol

Thirty-two healthy asymptomatic volunteers without history of cardiovascular disease, stroke, transient ischemic attack or dementia and without cardiovascular medication were included. The characteristics of the study population are summarized in Table 1. Mean systolic blood pressure was 124 ± 12 mmHg and mean diastolic blood pressure was 75 ± 8 mmHg. Mean heart rate was 62 ± 9 beats/minute and all volunteers were in

1 regular sinus rhythm. Fifteen volunteers (47%) were male. Mean BMI was 23.0 ± 2.2 kg/
2 m^2 . Approval from the local medical ethics committee was obtained and all subjects
3 gave written informed consent. Part of the data of this study group has been published
4 before in a study focusing on age-relation and PWV leveling.

5 Subjects underwent 3T MRI examination (Achieva, Philips Medical Systems, Best, The
6 Netherlands) between August 2011 and March 2012 to assess PWV in the aortic arch
7 and the carotid artery and measurements for aorta and carotid artery vessel wall area
8 (VWA) using validated MRI techniques. The relation between functional (PWV_{AO} in the
9 aorta and PWV_{CA} in the carotid artery) and morphologic measures (VWA_{AO} in the aorta
10 and VWA_{CA} in the carotid artery) within the same vascular territory and across vascular
11 territories was assessed.

12
13 **Table 1:** Characteristics of study population (n=32)

14 Male/Female	15/17
15 Age (years)	41 ± 16 (range: 20 – 68 years)
16 Systolic blood pressure (mmHg)	124 ± 12
17 Diastolic blood pressure (mmHg)	75 ± 8
18 Heart rate (beats/minute)	62 ± 9
19 BMI (kg/m^2)	23 ± 2
20 BSA (m^2)	1.9 ± 0.2
21 Aortic flow volume per minute/BSA ($ml/min/m^2$)	2936 ± 724

22 Data are represented as mean $\pm$ standard deviation or median (range).
23 Abbreviations: BMI: body mass index, BSA: body surface area.

24
25 **MRI Acquisition**

26
27 *Aortic and carotid arterial pulse wave velocity*

28 Using a dedicated cardiac coil (6-element phased-array coil), PWV_{AO} was assessed by
29 means of one through-plane VE MRI acquisition perpendicular to the aorta, at the level
30 of the pulmonary artery, transecting both the ascending and proximal descending aorta
31 (Figure 1 A1) to assess the blood flow velocity (Figure 1 A2) (12).

32 Scan parameters VE MRI acquisition: field-of-view (FOV) 320×260 mm^2 , slice thickness
33 8 mm, flip angle (FA) 10° , repetition time (TR) 4.9 ms, echo time (TE) 2.9 ms, acquisition
34 resolution $2.5 \times 2.5 \times 8.0$ mm^3 , number of signal averages (NSA) 1, velocity sensitivity (V_{enc})
35 150 cm/s in through-plane direction. The true maximal temporal resolution (TRes, de-
36 fined as $2 \times TR$) amounted to 9.8 ms. Vector ECG-triggering with retrospective gating was
37 used with maximal number of phases reconstructed. Scan duration depended on the
38 subject's heart rate and was approximately 2 minutes at 60 beats per minute heart rate.

39 Using a 16-element neurovascular head-neck coil, PWV in the carotid artery (PWV_{CA})
40 was assessed by means of two consecutive through-plane VE MRI acquisitions, planned
41 perpendicular to the left carotid artery using a rotational maximal-intensity-projection
42 (MIP) of a three-dimensional (3D) time-of-flight registration of the carotid circulation,

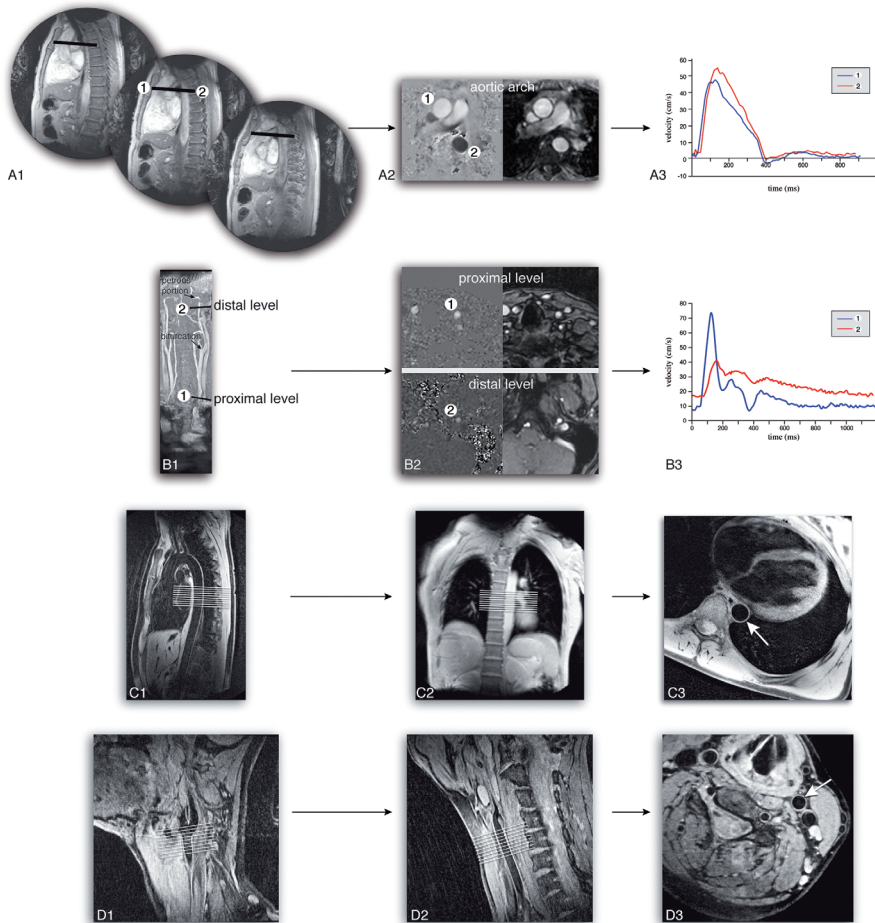


Figure 1. Representation of methods for pulse wave velocity and vessel wall area assessment, both for the aorta (AO) and the carotid artery (CA). **(A)** PWV_{AO} was assessed by means of one through-plane velocity-encoded MRI acquisition, planned at the level of the pulmonary trunk, transecting both the ascending aorta (1) and proximal descending aorta (2) (**A1**), resulting in the following velocity-encoded images (**A2**). From the propagation of the velocity-time waveforms (**A3**), PWV_{AO} is determined.

(B) PWV_{CA} was assessed by means of two-slice through-plane velocity-encoded MRI at two locations, proximally at the left common carotid artery just above the aortic arch (1) and distally just below the petrous portion of the left internal carotid artery (2) (**B1**), which were planned on the rotational maximum-intensity-projection of a 3D Time-Of-Flight acquisition of the carotid arteries. The velocity-encoded images acquired in the carotid artery are represented in (**B2**). From the propagation of the velocity waveforms (**B3**), PWV_{CA} is determined.

(C) VWA_{AO} was determined with a 2 cm thick 3-dimensional volume acquisition (in white) consisting of 10 slices positioned on two aortic survey scans; a double-oblique sagittal black-blood image of the aorta (**C1**) and double-oblique coronal bright-blood image of the aorta (**C2**). From the resulting cross-sectional black-blood images of the aorta (**C3**, aorta is indicated by white arrow), VWA_{AO} is determined.

(D) VWA_{CA} was determined with a 1.6 cm multi-slice 2-dimensional acquisition stack (in white) consisting of 9 slices positioned on two carotid artery survey scans; a double-oblique sagittal black-blood image of the carotid artery (**D1**) and a double-oblique coronal image of the carotid artery (**D2**). From the resulting cross-sectional black-blood images of the carotid artery (**D3**, carotid artery is indicated by white arrow), VWA_{CA} is determined.

to assess the blood flow velocity (Figure 1 B1,2). The first acquisition was positioned proximally at the origin of the common carotid artery, just above the aortic arch and the second acquisition was positioned distal to the bifurcation and just below the petrous portion of the internal carotid artery (Figure 1 B1).

Scan parameters 3D TOF: T1-weighted gradient-echo, FOV $180 \times 172 \text{ mm}^2$, 350 over-contiguous slices, slice thickness 2 mm, TR 23 ms, TE 3.45 ms, FA 15° , acquisition resolution: $1.0 \times 2.8 \times 2.0 \text{ mm}^3$.

Scan parameters VE acquisitions: FOV $200 \times 200 \text{ mm}^2$, slice thickness 5 mm, FA 10° , TR 6.2 ms, TE 3.4 ms, acquisition resolution $1.52 \times 1.50 \times 5.0 \text{ mm}^3$, NSA 1, V_{enc} was 150 cm/s for first acquisition at the common carotid artery and V_{enc} was 120 cm/s for the second acquisition at the internal carotid artery, with velocity encoding both in through-plane direction. TRes amounted to 12.4 ms. Vector ECG-triggering with retrospective gating was used with the maximal number of phases reconstructed. Scan duration depended on the subject's heart rate and was approximately 2 minutes for each acquisition.

Aortic and carotid vessel wall area

VWA_{AO} was determined using a standardized scan protocol, which was described before (10). Briefly, a 3D dual-inversion-recovery black-blood segmented k-space gradient-echo imaging sequence with fat suppression was planned perpendicular to both a sagittal (Figure 1 C1) and coronal view (Figure 1 C2) of the aorta and was reconstructed into 10 cross-sectional slices of 2 mm (Figure 1 C3) (13). The upper level of the 3D volume slab was positioned at the level of the upper edge of the eight thoracic vertebra. Scan parameters: FOV $270 \times 203 \text{ mm}^2$, slice thickness 2 mm, FA 20° , TR 4.9 ms, TE 2.5 ms, acquisition resolution $0.53 \times 0.53 \times 2.0 \text{ mm}^3$, NSA 2. Vector ECG-triggering at end-diastole was used. Data were acquired at every other heartbeat to suppress signal of slow blood flow in the lumen. Respiratory motion suppression was achieved by navigator gating with a 5 mm gating window, positioned at the top of the hemi-diaphragm (10). Scan duration depended on heart rate and navigator efficiency and was approximately 6.5 minutes.

VWA_{CA} was determined using a standardized scan protocol, previously described in full (14). Briefly, a standard Philips SENSE-flex-M surface coil with two flexible elements of $14 \times 17 \text{ cm}$ was positioned around the neck. A 2D T1-weighted segmented gradient echo-sequence was planned on sagittal and coronal surveys scans (Figure 1 D1,2), perpendicular to the course of the common carotid artery in both views (Figure 1 D3). Nine contiguous transverse slices of 2 mm thickness were positioned perpendicular to the left common carotid artery, starting from the carotid bifurcation in the proximal (caudal) direction. Scan parameters: 2-dimensional (2D) black-blood T1-weighted fast gradient echo sequence, FOV $140 \times 140 \text{ mm}^2$, 2.0 mm slice thickness, FA 45° , TR 12.4 ms, TE 3.5 ms, acquired resolution $0.46 \times 0.46 \times 2.0 \text{ mm}^3$, NSA 2. Vector ECG-triggering at end-diastole was used. Scan duration depended on the subject's heart rate and was approximately 10 minutes (for 9 slices at a mean heart rate of 60 beats per minutes).

Image analysis

Aortic and carotid arterial pulse wave velocity

PWV_{AO} and PWV_{CA} were both determined by the transit-time method (15). Using MASS software (Leiden University Medical Center, Leiden, The Netherlands), the distance between two sampling sites (Δx) was manually determined by placing a poly-line along the vessel centerline.

This was performed for the aorta by using the sagittal survey images and for the carotid artery by using the rotational MIP of the TOF image. Using FLOW software (Leiden University Medical Center, Leiden, The Netherlands) with automated contour detection for image segmentation, wave propagation was evaluated from maximal velocity-time curves that were obtained at all sampling sites (Figure 1 A3, B3). The foot-to-foot definition was used for Δt (i.e., the transit-time)-assessment, with automated detection of the foot of the systolic velocity wave front (i.e., the wave arrival time). Accordingly, PWV was calculated as $\Delta x / \Delta t$ (m/s) (9).

Aortic and carotid vessel wall area

VWA analysis was performed using the VesselMass software (Leiden University Medical Center, Leiden, The Netherlands). Lumen and outer wall contours were detected as was previously described (16,17). For the aorta, contour segmentation was performed in eight slices out of ten. Both outer slices of the stack were disregarded as image quality may vary in the outer slices of a 3D image set due to band width drop-off. For the carotid artery, slices were excluded for analysis only at the distal part of the imaging stack, when the bifurcation of the carotid artery was already present in the image and possibly influencing analysis of common carotid artery vessel wall thickness. Contour segmentation was performed in at least three slices out of nine slices and a maximum of analyzed slices was six. The average vessel wall area is represented as cross-sectional area (mm²), averaged over all included slices. Consecutively, for both the aorta and the carotid artery, vessel wall was indexed for body surface area (BSA) (in mm²/m²), determined according to the Mosteller's formula (18).

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD). Univariable linear regression analyses were performed for the total study population to assess the associations between VWA and PWV. The values for VWA were not normally distributed and therefore log transformed to assess the association between VWA and PWV. Younger or older age (as binary variable) was included as an independent variable in the linear regression analyses to acquire age-adjusted regression lines. Regression lines and 95% CIs of the slope are reported. To assess the relative strength of the predictive values of VWA_{AO} and VWA_{CA} for PWV_{AO}, a forward selection model was used, with VWA_{AO} and VWA_{CA} as dependent variables and PWV_{AO} as independent variable. The predictive value of VWA_{AO} and VWA_{CA} for PWV_{CA} was similarly assessed.

RESULTS

Mean evaluated aortic arch trajectory was 115 ± 24 mm and mean evaluable left carotid artery trajectory was 174 ± 11 mm.

PWV and VWA of the aorta and carotid artery

Mean values for PWV and VWA are presented in Table 2. For the total study population, mean PWV_{AO} was not significantly different compared to mean PWV_{CA} (6.1 ± 1.7 m/s versus 6.3 ± 1.4 m/s, $p=0.55$).

Table 2: MRI results

Trajectory aorta (mm)	115 ± 24
Trajectory carotid artery (mm)	174 ± 11
PWV aorta (m/s)	6.1 ± 1.7
PWV carotid artery (m/s)	6.3 ± 1.4
Aorta vessel wall area/BSA (average per slice, mm^2/m^2)	47.1 (38.1 – 58)
Carotid artery vessel wall area/BSA (average per slice, mm^2/m^2)	12.7 (11.2 – 15.7)

Data are represented as mean $\pm$ standard deviation or as median (interquartile range).

Abbreviations: PWV: pulse wave velocity, BSA: body surface area.

Associations within the same vascular territory

The linear regression analyses between PWV and VWA within the same vascular territory are presented in Figure 2A,B for the aorta and carotid artery respectively. Significant correlations were observed between PWV and VWA within the same vascular territory (Table 3). For the aorta, the relation between PWV and VWA was influenced by age indicated by the reduced slope in the age-adjusted regression line. For the carotid artery, the observed association between PWV and VWA was less influenced by age.

Associations across vascular territories

The linear regression analyses between PWV and VWA across vascular territories are presented in Figure 3A,B. Across vascular territories, PWV and VWA were correlated (Table 3), but these associations were less strong when compared to the associations within vascular territories, both for the aorta ($r=0.71$, $p<0.0001$ for PWV_{AO} and VWA_{AO} versus $r=0.53$, $p=0.002$ for PWV_{AO} and VWA_{CA} , respectively) as well as for the carotid artery ($r=0.61$, $p<0.0001$ for PWV_{CA} and VWA_{CA} versus $r=0.46$, $p=0.008$ for PWV_{CA} and VWA_{AO}).

Finally, the association between PWV_{AO} and PWV_{CA} was statistically significant (Figure 4A) as well as the association between VWA_{AO} and VWA_{CA} (Figure 4B).

Moreover, in a forward selection model, VWA_{AO} was selected ($p<0.0001$) for prediction for PWV_{AO} , whereas VWA_{CA} was not independently associated ($p=0.6$) with PWV_{AO} after correction for VWA_{AO} . In addition, for predicting PWV_{CA} , VWA_{CA} ($p<0.0001$) was selected, whereas VWA_{AO} was not independently ($p=0.8$) associated with PWV_{CA} .

Figure 2-4. Linear regression analyses for the associations and the age-adjusted associations-between PWV and VWA. Values of VWA are plotted to a logarithmic scale.

Association PWV and VWA within the same vascular territory

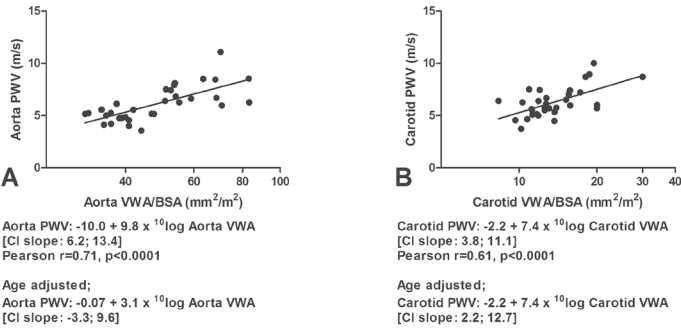


Figure 2A: PWV_{AO} and VWA_{AO} (i.e. within the same vascular territory). **Figure 2B:** PWV_{CA} and VWA_{CA} (i.e. within the same vascular territory).

Association PWV and VWA across vascular territories

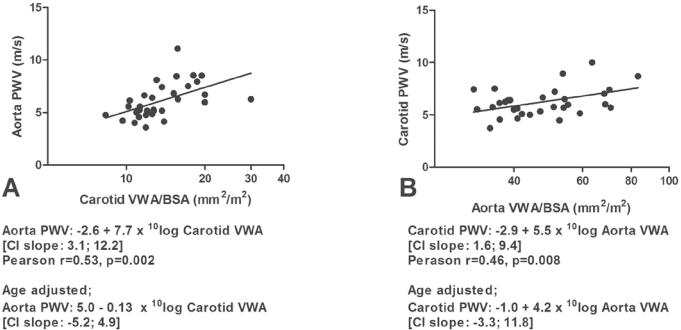


Figure 3A: PWV_{AO} and VWA_{CA} (i.e. across vascular territories). **Figure 3B:** PWV_{CA} and VWA_{AO} (i.e. across vascular territories).

Association Aorta and Carotid Artery

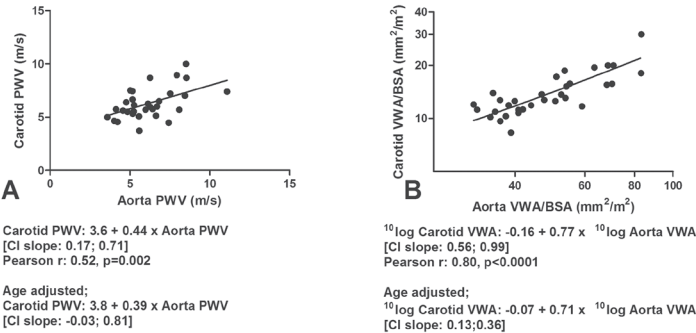


Figure 4A: PWV_{AO} and PWV_{CA}. **Figure 4B:** VWA_{AO} and VWA_{CA}.

Table 3: Correlation between vessel wall properties

	Aorta PWV	Carotid PWV	¹⁰ log Aorta VWA	¹⁰ log Carotid VWA
Aorta PWV	1	0.52 (0.002)	0.71 (<0.0001)	0.53 (0.002)
Carotid PWV	0.52 (0.002)	1	0.46 (0.008)	0.61 (p<0.0001)
¹⁰ log Aorta VWA	0.71 (<0.0001)	0.46 (0.008)	1	0.8 (<0.0001)
¹⁰ log Carotid VWA	0.53 (0.002)	0.61 (<0.0001)	0.8 (<0.0001)	1

Data are represented as Pearson correlation (p-value)

Abbreviations: PWV: pulse wave velocity, VWA: vessel wall area.

DISCUSSION

The current study demonstrated that morphologic and functional vessel wall properties in aorta and carotid artery are significantly associated. The main finding of our study is that this association was stronger within the same vascular territory, for both the aorta and the carotid artery, rather than across different vascular territories. To the best of our knowledge, our study is the first to report an evaluation of both VWA and PWV-assessment in the aorta as well as in the left carotid artery by using VE MRI.

Our findings highlight the potential of 3T MRI for non-invasive assessment of both PWV and VWA in the aorta and the carotid artery. Indeed, the assessment of arterial stiffness by PWV at various vascular territories to evaluate the predictive value for vascular events is of clinical interest (1,4,6).

Aortic stiffening is well-known to be associated with cardiovascular disease (1,12,19). However, recently it was suggested that the PWV-ratio between the aortic arch and the carotid artery may be an independent predictor for specific end-organ damage in the brain (4,6). With aging 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 brain microcirculation (3-5).

Previous studies almost exclusively used applanation tonometry and echo Doppler for arterial stiffness assessment (4,5,20,21). Both modalities can only provide an estimation of the global PWV in the whole aorta, due to the unavailability of appropriate acoustic windows to image the complete vascular tree, the inability of accurate determination of the wave propagation path length (7). MRI has several advantages over echo Doppler; it allows for precise measurement of this path length and direct sampling of aortic PWV and carotid arterial PWV over a longer trajectory (especially for the carotid artery) is possible, without any restriction regarding the choice of imaging plane.

Associations between PWV and VWA within the same vascular territory

Our study showed significant associations between PWV_{AO} and VWA_{AO} and between PWV_{CA} and VWA_{CA}. This coupling between wall morphology and function within the same vascular territory is in line with the concept of aortic stiffness described by the Moens-Korteweg equation, which describes a direct relation between local PWV and diameter, thickness and elastic properties of the vessel wall (1). Altered mechanical

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, or both mechanisms apply and may result in a self-perpetuating process (3,21). Interestingly, in the present study, the association between PWV and VWA within the aorta seemed more influenced by age than within the carotid artery. This finding is in line with a previous study describing that the aorta has a higher sensitivity to vascular aging, including incremental collagen content and calcification of the vessel wall media (22). Moreover, an arterial-specific age-relation of aortic and carotid arterial stiffness has been observed (5).

Associations between PWV and VWA across vascular territories

We also observed significant cross-link associations between PWV and VWA of the aorta and carotid artery. Our findings are in line with a previous study describing the association between aortic stiffness and increased carotid arterial intima-media thickness (IMT) (21). In atherosclerosis, gradual arterial changes are considered to be part of a diffuse systemic process, affecting different sites of the vascular tree. Therefore, associations between PWV and VWA across vascular territories are to be expected. However, for the aorta and the carotid artery, the association between PWV and VWA within the same vascular territory was stronger than the association between PWV and VWA across the vascular territories. This may suggest that sampling of IMT in the carotid artery might not be the most optimal measurement to assess the status of atherosclerosis in the aorta or in an even more remote vascular territory such as the peripheral arteries. Our finding is in line with a recent study by Brandts et al. (17), where in patients with hypertension, a stronger association was described between aortic PWV and aortic VWA than between aortic PWV and carotid VWA. In that study, PWV was only assessed for the aorta. Additionally, we present complete associations between PWV and VWA, in both the aorta as well as in the carotid artery. In our study, PWV_{CA} was significantly associated with both carotid artery VWA and with aorta VWA, but similar to the findings for the aorta, the strength of the association between PWV and VWA within the same vascular territory was stronger than across different vascular territories. Moreover, in forward selection models, only the site-specific VWA was selected for prediction of PWV. The stronger association between morphology and function within the same vascular territory as compared to the association across vascular territories is in line with the concept of arterial specific vascular aging.

Limitations

Our study has some limitations. First, it involves a cross-sectional design in a relatively small selective population of healthy volunteers. Follow-up studies are needed to further elucidate the associations between aortic and carotid arterial PWV and VWA in a large cohort of normal volunteers and in different patient populations. Moreover, for comparison purposes, sampling of VWA was standardized to a limited selected segment of 1.6 cm for the carotid artery and 2 cm for the aorta. Increasing the segment trajectory

length or adding segments at other parts of the aorta and carotid artery is of course feasible at the penalty of an increasing acquisition time.

Second, assessment of PWV_{CA} by VE MRI has not been validated against invasive pressure measurements, as was previously done for PWV_{AO} (9). However, the same imaging technique and image processing strategy were followed as for the well-validated PWV_{AO} -assessment.

Moreover, PWV -assessment using MRI is time-consuming and relatively expensive in comparison to echocardiography. However, previous studies using echocardiography only used carotid arterial IMT measurements as surrogate marker of generalized atherosclerosis, whereas MRI allows for site-specific sampling, since it is not restricted regarding the choice of imaging plane, i.e. measuring the aorta in patients with site-specific *subclinical* atherosclerosis in the aorta.

Conclusion

In conclusion, we have demonstrated that functional and morphologic vessel wall properties in aorta and carotid artery were significantly stronger associated when sampled within the same vascular territory rather than across different vascular territories, reflecting site-specific coupling of cross-sectional vessel wall area and function.

REFERENCES

1. Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness current understanding and future directions. *J Am Coll Cardiol* 2011;57:1511-1522.
2. Lloyd-Jones D, Adams RJ, Brown TM et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* 2010;121:e46-e215.
3. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a “set up” for vascular disease. *Circulation* 2003;107:139-146.
4. Mitchell GF, van Buchem MA, Sigurdsson S et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility—Reykjavik study. *Brain* 2011;134:3398-3407.
5. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *J Appl Physiol* 2008;105:1652-1660.
6. King KS, Chen KX, Hulsey KM et al. White matter hyperintensities: use of aortic arch pulse wave velocity to predict volume independent of other cardiovascular risk factors. *Radiology* 2013;267:709-717.
7. Corti R, Fuster V. Imaging of atherosclerosis: magnetic resonance imaging. *Eur Heart J* 2011;32:1709-1719.
8. Fayad ZA, Mani V, Fuster V. The time has come for clinical cardiovascular trials with plaque characterization as an endpoint. *Eur Heart J* 2012;33:160-161.
9. Grotenhuis HB, Westenberg JJ, Steendijk P et al. Validation and reproducibility of aortic pulse wave velocity as assessed with velocity-encoded MRI. *J Magn Reson Imaging* 2009;30:521-526.
10. Roes SD, Westenberg JJ, Doornbos J et al. Aortic vessel wall magnetic resonance imaging at 3.0 Tesla: a reproducibility study of respiratory navigator gated free-breathing 3D black blood magnetic resonance imaging. *Magn Reson Med* 2009;61:35-44.
11. Kroner ES, van der Geest RJ, Scholte AJ et al. Evaluation of sampling density on the accuracy of aortic pulse wave velocity from velocity-encoded MRI in patients with Marfan syndrome. *J Magn Reson Imaging* 2012;36:1470-1476.
12. Brandts A, van Elderen SG, Westenberg JJ et al. Association of aortic arch pulse wave velocity with left ventricular mass and lacunar brain infarcts in hypertensive patients: assessment with MR imaging. *Radiology* 2009;253:681-688.
13. Edelman RR, Chien D, Kim D. Fast selective black blood MR imaging. *Radiology* 1991;181:655-660.
14. Alizadeh DR, Doornbos J, Tamsma JT et al. Assessment of the carotid artery by MRI at 3T: a study on reproducibility. *J Magn Reson Imaging* 2007;25:1035-1043.
15. Westenberg JJ, de Roos A, Grotenhuis HB et al. Improved aortic pulse wave velocity assessment from multislice two-directional in-plane velocity-encoded magnetic resonance imaging. *J Magn Reson Imaging* 2010;32:1086-1094.
16. Adame IM, van der Geest RJ, Wasserman BA, Mohamed MA, Reiber JH, Lelieveldt BP. Automatic segmentation and plaque characterization in atherosclerotic carotid artery MR images. *MAGMA* 2004;16:227-234.
17. Brandts A, Westenberg JJ, van Elderen SG et al. Site-specific coupling between vascular wall thickness and function: an observational MRI study of vessel wall thickening and stiffening in hypertension. *Invest Radiol* 2013;48:86-91.
18. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987;317:1098.

19. van Elderen SG, Brandts A, Westenberg JJ et al. Aortic stiffness is associated with cardiac function and cerebral small vessel disease in patients with type 1 diabetes mellitus: assessment by magnetic resonance imaging. *Eur Radiol* 2010;20:1132-1138.
20. Mitchell JR, Schwartz CJ. Relationship between arterial disease in different sites. A study of the aorta and coronary, carotid, and iliac arteries. *Br Med J* 1962;1:1293-1301.
21. van Popele NM, Grobbee DE, Bots ML et al. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke* 2001;32:454-460.
22. Paini A, Boutouyrie P, Calvet D, Tropeano AI, Laloux B, Laurent S. Carotid and aortic stiffness: determinants of discrepancies. *Hypertension* 2006;47:371-37

CHAPTER 9

MORPHOLOGICAL AND FUNCTIONAL CAROTID VESSEL WALL PROPERTIES IN RELATION TO CEREBRAL WHITE MATTER LESIONS IN MYOCARDIAL INFARCTION PATIENTS

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Neth Heart J 2015; in press



ABSTRACT

Purpose: Atherosclerotic *large* vessel disease is potentially involved in the pathogenesis of cerebral *small* vessel disease related to occurrence of white matter lesions (WMLs) in the brain. We aimed to assess morphological and functional carotid vessel wall properties in relation to WML using magnetic resonance imaging (MRI) in myocardial infarction (MI) patients.

Methods: Twenty MI patients (90% male, 61 ± 11 years) underwent carotid artery and brain MRI. Carotid vessel wall thickness (VWT) was assessed, by detecting lumen and outerwall contours. Carotid pulse wave velocity (PWV), a measure of elasticity, was determined using the transit-time method. Patients were divided according to the median VWT into two groups. Brain MRI allowed for the WML score.

Results: Mean VWT was 1.41 ± 0.29 mm and mean carotid pulse wave velocity was 7.0 ± 2.2 m/s. A significant correlation (Pearson $r=0.45$, $p=0.046$) between VWT and PWV was observed. Furthermore, in the group of high VWT, the median WML score was higher as compared to the group with lower VWT (4.0 vs 3.0, $p=0.035$).

Conclusions: Carotid artery morphological and functional alterations are correlated in MI patients. Patients with high VWT showed higher amount of periventricular WMLs. These findings support the hypothesis that atherosclerotic *large* vessel disease is potentially involved in the pathogenesis of cerebral *small* vessel disease.

INTRODUCTION

Vascular risk exposure and age exert systemic effects on both morphology and function of the arterial vessel wall by degeneration of the aortic media and breakdown of elastic fibers (1). Accordingly, in patients with established atherosclerotic disease, e.g. patients with a previous myocardial infarction (MI), accelerated morphological changes are considered to be associated with increased arterial stiffness. Moreover, atherosclerotic *large* vessel disease is potentially involved in the pathogenesis of cerebral white matter lesions (WMLs) that are generally regarded as manifestations of cerebral *small* vessel disease (2-4). Indeed, it is hypothesized that pathologically increased arterial stiffness results in deficient absorption of the pulse wave travelling through the vascular system. A deficient absorption of the systolic pulse wave may result in transmission of high pulsatile flow from the aorta towards the carotid artery and the brain, potentially initiating carotid vessel wall remodeling and functional changes which may lead to the development of cerebral small vessel disease and subsequent WMLs. Accordingly, the association between systemic *large* vessel disease, cerebral *small* vessel disease and WMLs in MI patients is of interest.

Non-invasive evaluation of morphologic and functional vessel wall properties and cerebral WMLs is feasible using a comprehensive magnetic resonance imaging (MRI) approach (5-7). Still, very little is known about the direct association between carotid vessel wall thickness (VWT), vascular stiffness and white matter brain lesions in MI patients. Therefore, the purpose of this study was to assess the association between morphological and functional carotid vessel wall properties and cerebral periventricular WML in myocardial infarction (MI) patients using MRI.

MATERIALS AND METHODS

Population and study protocol

Twenty MI patients (90% male, 61 ± 11 years old) who previously suffered a myocardial infarction (MI) were included. Approval from the local medical ethics committee was obtained and all patients gave written informed consent. Patients underwent 3T MRI-examinations (Philips Achieva Philips Medical Systems, Best, The Netherlands) between October 2011 and November 2012. Carotid artery VWT, pulse wave velocity (PWV) in the carotid artery and cerebral WMLs were assessed using MRI techniques (7-9) (Figure 1).

MRI Acquisition

Carotid vessel wall thickness

Carotid VWT was determined using a 2D T1-weighted segmented gradient echo-sequence using a standard Philips SENSE-flex-M surface coil with two flexible elements of 14×17 cm as previously described (5).

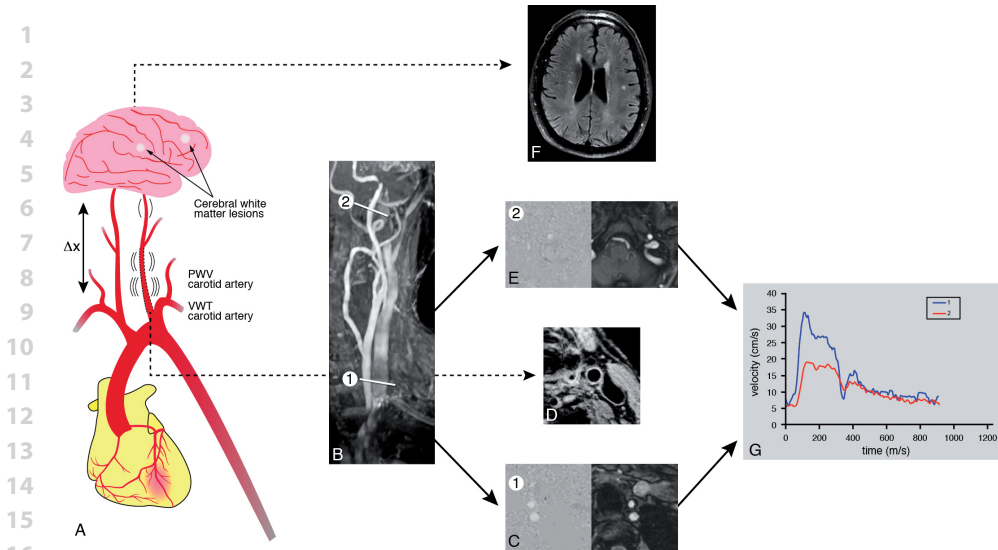


Figure 1. A schematic representation of the study protocol (**Figure 1 A**). Carotid vessel wall properties (vessel wall thickness (VWT) and pulse wave velocity (PWV)) and cerebral periventricular white matter lesions (WML) were assessed in myocardial infarction patients.

PWV was assessed at two locations, proximally at the left common carotid artery just above the aortic arch (1) and distally just below the petrous portion of the left internal carotid artery (2), which were planned on the rotational maximum-intensity-projection of a 3D Time-Of-Flight acquisition of the carotid arteries (**Figure 1 B**). The corresponding velocity-encoded images are represented in **Figure 1 C, E** for the proximal and distal acquisition respectively. From the propagation of the velocity waveforms (**Figure 1 G**), PWV is determined. VWT was assessed at the left common carotid artery (4-mm proximal to the carotid bifurcation) (**Figure 1 D**). Cerebral WML were determined using spin-echo T2-weighted and a fluid-attenuated inversion recovery (**Figure 1 F**).

Scan parameters: 2-dimensional (2D) BB T1-weighted fast gradient echo sequence, FOV $140 \times 140 \text{ mm}^2$, 2.0 mm slice thickness, FA 45° , TR 12.4ms, TE 3.5ms, acquired resolution $0.46 \times 0.46 \times 2.0 \text{ mm}^3$, NSA 2. Acquisitions were gated at end-diastole using vector ECG.

Carotid pulse wave velocity

Carotid PWV was assessed by two consecutive VE MRI acquisitions using a 16-element neurovascular head-neck coil as previously described (8). The first acquisition (proximal) was planned perpendicular to the left carotid artery at the level of the origin of the common carotid artery and the second (distal), at the level of the internal carotid artery, below the petrous segment (**Figure 1 B, C, E**).

Scan parameters were: FOV $200 \times 200 \text{ mm}^2$, slice thickness 5 mm, FA 10° , TR 6.2 ms, TE 3.4 ms, acquisition resolution $1.52 \times 1.50 \times 5.0 \text{ mm}^3$, NSA 1, V_{enc} for the proximal acquisition 150 cm/s and distal acquisition 120 cm/s, both in through-plane direction. The true temporal resolution (TRes, defined as $2 \times \text{TR}$, amounted to 12.4 ms per heart phase). Retrospective gating using vector ECG triggering was used

Cerebral white matter lesions

Cerebral WMLs were determined using spin-echo T2-weighted and a fluid-attenuated inversion recovery (FLAIR) sequences as previously described (10). Scan parameters for T2-weighted imaging: FOV 224×180mm², matrix size 448×320, 40 transverse slices without gap, 3.6 mm slice thickness, FA 90°, TR 4200 ms, TE 80 ms. Scan parameters for FLAIR sequence: FOV 220×176mm², matrix size: 320×240, 25 transverse slices without gap, 5 mm slice thickness, FA 90°, TR 11 000 ms, TE 125 ms (10).

Image analysis

Carotid vessel wall thickness

Contour segmentation was performed on a slice of the left common carotid artery (4-mm proximal to the carotid bifurcation) using Vessel MASS software (Leiden University Medical Center, Leiden, the Netherlands) as previously described (11) (Figure 1D). Mean and maximal carotid vessel wall thickness (mm) were evaluated. Contour segmentation was performed by a researcher with three years of experience in cardiac MRI.

Pulse wave velocity

Carotid PWV was obtained from the VE MRI data (7,8). The carotid artery path length (Δx) between subsequent proximal and distal carotid artery sampling sites was manually determined. Wave propagation was evaluated from maximal velocity-time curves that were obtained by using FLOW software (Leiden University Medical Center, Leiden, The Netherlands) with automated contour detection for image segmentation. The foot-to-foot definition was used for Δt (i.e., the transit-time)-assessment; with automated detection of the foot of the systolic velocity wave front (i.e., the wave arrival time). Accordingly, carotid pulse wave velocity was calculated as $\Delta x / \Delta t$ (m/s) (Figure 1G).

White matter lesions

White matter hyper-intensities/ lesions were defined as areas within the cerebral white matter, with increased signal on both T2-weighted images and FLAIR images without mass effect (10) (Figure 1F). WMLs were rated according to a slightly modified version of the semi-quantitative rating scale of Scheltens et al., as previously described (10,12). Periventricular and subcortical WMLs were rated separately. Periventricular WMLs for three separate regions (anterior, lateral, posterior) were scored as: no white matter lesions (0); normal amount of white matter lesions (1); abnormal amount (2); very abnormal amount (3) (12). Next, a total periventricular WMLs score was calculated as the sum of the three individual scores.

Subcortical WMLs were scored as: no white matter lesions (0); 1-3 small lesions (1); >3 small lesions (2); very abnormal, confluent lesions (3) (12).

WML were scored by a researcher (JvdG) with 15 years of experience in neuroradiology.

1 Statistical analysis

2 Statistical analysis was performed using SPSS for Windows (version 18.0; SPSS, Chicago,
3 Illinois, USA). Data are expressed as mean $\pm$ standard deviations (SD) unless stated
4 otherwise.

5 The relation between and morphologic measurements (VWT in the carotid artery) and
6 functional properties (i.e. PWV of the carotid artery) was assessed. Next, the association
7 between vessel wall parameters and WMLs was investigated.

8 The association between mean and maximal carotid VWT and carotid PWV was as-
9 sessed using linear regression.

10 Multivariate linear regression analysis with PWV as independent variable and VWT and
11 age as dependent variables was performed to assess influence of age on the association
12 between VWT and PWV.

13 Next, patients were divided into groups according to the median of VWT. Carotid
14 PWV as well as the total amount of periventricular and subcortical WMLs was compared
15 (using the Mann-Whitney Test) between the group with high VWT ($>$ median VWT) as
16 compared to the group with low VWT ($\leq$ median VWT).

19 RESULTS

21 Patient characteristics and results are presented in Table 1. Twenty MI patients (18
22 male, 2 female, mean age 61 ± 11 years) were included. All patients were prescribed
23 medication for secondary prevention of MI (i.e anticoagulants and or platelet inhibitors,
24 beta-blockers, angiotensin-converting-enzyme inhibitors or angiotensin II inhibitors
25 and statins) according to clinical guidelines (13).

27 Vessel wall morphology and function

28 MRI measurements are presented in Table 2. Mean carotid vessel wall thickness was 1.41
29 ± 0.29 mm and mean carotid PWV 7.0 ± 2.2 m/s.

30 Interestingly, PWV of the carotid artery was significantly correlated with VWT of the
31 carotid artery (Pearson $r=0.45$, $P=0.046$). The associations between PWV of the carotid
32 artery and mean and maximal VWT is presented in Figure 2A and 2B. Also, the influ-
33 ence of age on the association between PWV and VWT is shown. Age sharpened the
34 association between vessel wall thickness and pulse wave velocity. However, age was
35 not a statistically significant predictor in the multiple regression model.

37 White matter lesions

38 In 15 out of the 20 patients, also brain MRI was acquired. Five (33%) patients showed an
39 abnormal amount of periventricular WMLs ($n=5$), according to the modified Scheltens
40 score. Twelve (80%) patients were diagnosed with the presence of subcortical WMLs.

41 Detailed scores for anatomical subdivision are provided in Table 3.

Table 1 Characteristics and results of study population (n=20)

Age at MRI, years	61 ±11
Age range (min – max)	(37 – 82)
Days between myocardial infarction and vessel wall MRI scan (days)	299 ±144
Culprit vessel at myocardial infarction	
Left anterior descending artery	5 (25%)
Right coronary artery	13 (65%)
Circumflex artery	2 (10%)
Peak troponin T values (µg/l)	3.8 ±2.4
Male gender, n (%)	18 (90%)
BMI (kg/m ²)	26 ±3
Brachial blood pressure (mmHg)	
Systolic	125 ±23
Diastolic	76 ±12
Heart rate (beats per minute)	74 ±16
Patients with arterial hypertension, n (%)	10 (50%)
Patients with diabetes mellitus, n (%)	2 (10%)
Smokers, n (%)	8 (40%)
Total cholesterol (mmol/l)	5.09 ±1.17

Data are represented as mean ± standard deviation.

Abbreviations: MI: myocardial infarction, BMI: body mass index.

Table 2 MRI carotid vessel wall (n=20)

	MI patients (n=20)
Trajectory carotid artery, mm	147 ± 20
PWV carotid artery, m/s	7.0 ± 2.2
Mean vessel wall thickness carotid artery, mm	1.41 ± 0.3
Maximal vessel wall thickness carotid artery, mm	1.73 ± 0.4

Data are represented as mean ± standard deviation.

Abbreviations: PWV: pulse wave velocity.

Association vessel wall thickness, pulse wave velocity and white matter lesions

In patients with high VWT (>median VWT), a borderline significant higher carotid PWV (7.1 m/s versus 5.98 m/s, $p=0.07$) as compared to the patients with low vessel wall thickness was observed (Figure 2C). Furthermore, the total periventricular WMLs score was significant higher in the patients with high vessel wall thickness as compared to patients with low vessel wall thickness (4.0 versus 3.0 $p=0.035$) (Figure 2D)

In patients with high VWT, the total subcortical WMLs score was similar as compared to patients with low VWT (2.0 versus 1.0, $p=0.3$).

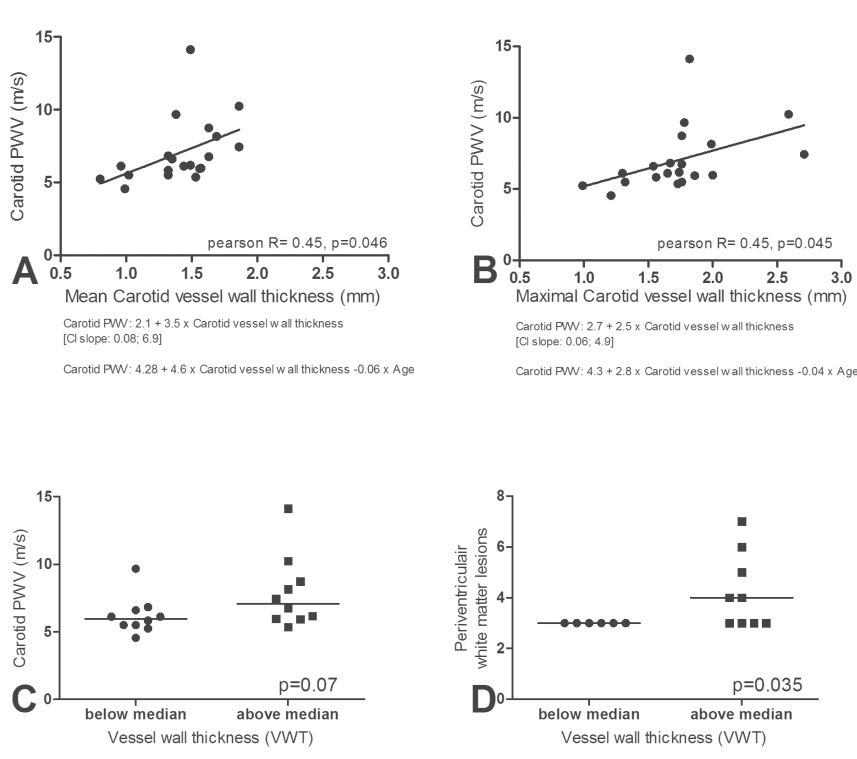


Figure 2. Association between carotid artery pulse wave velocity and mean- and maximal carotid vessel wall thickness in MI patients (A,B). Comparison of carotid pulse wave velocity and white matter lesions in patients with low versus high carotid vessel wall thickness (C,D).

Table 3 MRI white matter lesions(n=15)

	Periventricular lesion score			Subcortical lesion score
	Anterior	Lateral	Posterior	
Score 0	0 (0)	0 (0)	0 (0)	3 (20)
Score 1	11 (73)	11 (73)	14 (93)	5 (33)
Score 2	3 (20)	3 (20)	1 (7)	6 (40)
Score 3	1 (7)	1 (7)	0 (0)	1 (7)

Data are presented as number (percentage).

DISCUSSION

The present study evaluated the association between carotid morphological and functional imaging parameters and cerebral WML in patients after MI. The main findings of

our study are: (i) carotid VWT and carotid PWV are statistically significantly correlated in MI patients, and (ii) the total periventricular WMLs score was higher in the MI patients with high carotid vessel wall thickness versus the patients with low carotid VWT.

To the best of our knowledge, our study is the first to report an evaluation of both carotid VWT and PWV and cerebral WMLs in MI patients using a comprehensive MRI evaluation.

The assessment of VWT and PWV by MRI correlates to presence of WMLs, which is of clinical interest. Previous studies used echo (Doppler) for the assessment of VWT and arterial stiffness (14-16). This imaging technique is restricted by the choice of imaging plane (i.e. only sampling in the common carotid artery is possible). In contrast, MRI allows for direct sampling of VWT and PWV, without restrictions regarding the choice of imaging plane, thereby allowing sampling along the carotid arterial trajectory from the common carotid artery into the internal carotid artery. A recent MRI study by Corti et al. showed a decrement in carotid vessel wall area and maximal carotid artery thickness, but not minimal carotid artery thickness in hypercholesterolemic patients after statin use (17). We aimed to explore not only the morphological vessel wall changes but also the association between morphological and functional properties of the vessel wall.

Vessel wall morphology and function

Our study showed a significant association between mean and maximal VWT and PWV in the carotid artery in patients after MI. Our findings are consistent with a previous population-based cohort study by van Popele et al., who found increased common carotid stiffness assessed by ultrasound, in the highest quartile of intima-media thickness of the common carotid artery (15). Interestingly, our results indicate that morphology and functional parameters remain clearly associated in patients with established atherosclerotic disease. We also observed that age influenced the association between VWT and PWV. This finding is in line with previous studies describing increased carotid artery stiffening with age (2,14). Of note, in the present study age was not a statistically significant predictor in the multiple regression model. This could potentially be explained by the relatively small study group. Accordingly, future studies remain needed to further assess upon the influence of age on the association between vessel wall morphology and function in patients with established atherosclerotic disease.

White matter lesions

The prevalence of WMLs observed in the present study is in line with previous studies (10,18). A high prevalence of WMLs in MI patients is indeed to be expected, since risk factors associated with a MI are also risk factors for cerebral small vessel disease (19).

Increased vessel wall thickness and white matter lesions

Our study revealed that in MI patients with high VWT, the amount of periventricular WMLs was significantly higher as compared to subjects without increased VWT. Our findings are in line with a previous study in a population-based cohort (n=640, age: 59=71 years), describing the association between carotid atherosclerosis assessed by ultraso-

nography and WMLs (20). Moreover, Kwee et al. showed that in TIA/stroke patients with carotid artery stenosis, carotid plaque burden and WML severity was associated (21). Our results indicate that carotid VWT and WMLs are associated not only in the elderly general population, or TIA/stroke patients but also in patients with a previous MI.

In contrast to the result for periventricular WMLs, no relation between carotid vessel wall thickness and subcortical WMLs was observed. This difference is in line with a previous study (22) and may be explained to be the result of hypo-perfusion that can be caused by large vessel disease. Due to differences in blood supply the periventricular white matter is more vulnerable to a decrease in cerebral blood flow (10,22).

The current study showed associations between morphological and functional carotid vessel wall properties and cerebral white matter lesions in MI patients. The presence of WMLs in MI patients may have relevant clinical implications, since WMLs have been suggested to increase the risk of stroke and cognitive decline (18). However, it is not likely that MR imaging of the brain will be a routine investigation in MI patients. But, for identification of MI patients at risk, carotid vessel wall parameters might become beneficial in the future.

Limitations

Our study has some limitations. First, it involves a *cross-sectional* design in a relative small group of patients (n=20), of which 15 underwent brain MRI.

Follow-up studies are needed to further elucidate pathophysiological mechanisms between large vessel atherosclerosis and small vessel disease in patients with established atherosclerotic disease.

Furthermore, the comprehensive MRI evaluation of the present study is time-consuming and relative expensive in comparison to echocardiography. But for serial assessment of both vessel wall parameters and WML, MRI allows for a non-invasive, reproducible evaluation without restriction regarding imaging plane.

Conclusion

Morphological and functional alterations in the carotid artery are significantly correlated in MI patients. Patients with high carotid VWT showed higher amount of periventricular WMLs. These findings support the hypothesis that atherosclerotic *large* vessel disease is potentially involved in the pathogenesis of cerebral *small* vessel disease.

REFERENCES

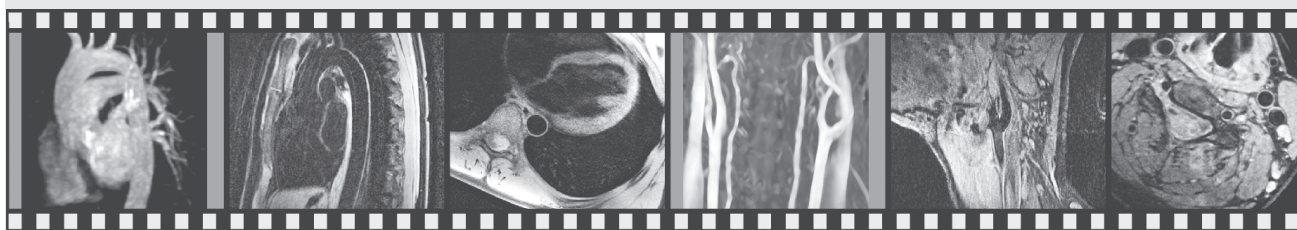
1. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. *Circulation* 2003;107:139-146.
2. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *J Appl Physiol* 2008;105:1652-1660.
3. Mitchell GF, van Buchem MA, Sigurdsson S et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility—Reykjavik study. *Brain* 2011;134:3398-3407.
4. Ritz K, van Buchem MA, Daemen MJ. The heart-brain connection: mechanistic insights and models. *Neth Heart J* 2013;21:55-57.
5. Alizadeh DR, Doornbos J, Tamsma JT et al. Assessment of the carotid artery by MRI at 3T: a study on reproducibility. *J Magn Reson Imaging* 2007;25:1035-1043.
6. van der Wall EE. Crown years for non-invasive cardiovascular imaging (Part III): 30 years cardiovascular magnetic resonance. *Neth Heart J* 2013;21:263-265.
7. Westenberg JJ, de Roos A, Grotenhuis HB et al. Improved aortic pulse wave velocity assessment from multislice two-directional in-plane velocity-encoded magnetic resonance imaging. *J Magn Reson Imaging* 2010;32:1086-1094.
8. Kroner ES, Lamb HJ, Siebelink HM et al. Pulse wave velocity and flow in the carotid artery versus the aortic arch: Effects of aging. *J Magn Reson Imaging* 2013.
9. Kroner ES, Lamb HJ, Siebelink HM et al. Coupling of vessel wall morphology and function in the aorta and the carotid artery: an evaluation with MRI. *Int J Cardiovasc Imaging* 2014;30:91-98.
10. Altmann-Schneider I, van der Grond J, Slagboom PE et al. Lower susceptibility to cerebral small vessel disease in human familial longevity: the Leiden Longevity Study. *Stroke* 2013;44:9-14.
11. Kroner ES, van Schinkel LD, Versluis MJ et al. Ultrahigh-field 7-T magnetic resonance carotid vessel wall imaging: initial experience in comparison with 3-T field strength. *Invest Radiol* 2012;47:697-704.
12. Scheltens P, Barkhof F, Leys D et al. A semiquantitative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *J Neurol Sci* 1993;114:7-12.
13. Liem SS, van der Hoeven BL, Oemrawsingh PV et al. MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. *Am Heart J* 2007;153:14-11.
14. Paini A, Boutouyrie P, Calvet D, Tropeano AI, Laloux B, Laurent S. Carotid and aortic stiffness: determinants of discrepancies. *Hypertension* 2006;47:371-376.
15. van Popele NM, Grobbee DE, Bots ML et al. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke* 2001;32:454-460.
16. Erqou S, Kip KE, Mulukutla SR, Aiyer AN, Reis SE. Racial differences in the burden of coronary artery calcium and carotid intima media thickness between Blacks and Whites. *Neth Heart J* 2015;23:44-51.
17. Corti R, Osende JI, Fayad ZA et al. In vivo noninvasive detection and age definition of arterial thrombus by MRI. *J Am Coll Cardiol* 2002;39:1366-1373.
18. Gerdes VE, Kwa VI, ten CH, Brandjes DP, Buller HR, Stam J. Cerebral white matter lesions predict both ischemic strokes and myocardial infarctions in patients with established atherosclerotic disease. *Atherosclerosis* 2006;186:166-172.
19. Remmelink M, Sjaauw KD, Yong ZY et al. Coronary microcirculatory dysfunction is associated with left ventricular dysfunction during follow-up after STEMI. *Neth Heart J* 2013;21:238-244.

20. Pico F, Dufouil C, Levy C et al. Longitudinal study of carotid atherosclerosis and white matter hyperintensities: the EVA-MRI cohort. *Cerebrovasc Dis* 2002;14:109-115.
21. Kwee RM, Hofman PA, Gronenschild EH et al. Association between carotid plaque characteristics and cerebral white matter lesions: one-year follow-up study by MRI. *PLoS One* 2011;6:e17070.
22. de Leeuw FE, de Groot JC, Bots ML et al. Carotid atherosclerosis and cerebral white matter lesions in a population based magnetic resonance imaging study. *J Neurol* 2000;247:291-296.

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CHAPTER 10

SUMMARY AND CONCLUSIONS



SUMMARY

The aim of this thesis was to assess morphological and functional vessel wall properties with various MRI techniques in different clinical settings.

The general introduction (**Chapter 1**) of this thesis provides general information about morphologic (i.e. atherosclerosis) and functional (i.e. impaired elasticity) changes of the vessel wall that play an important role in the development of cardiovascular disease and the potential of MRI 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.

Part I of the thesis focused on imaging of vessel wall morphology using MRI. Secondly, vessel wall function and its predictive value were evaluated in patients with the Marfan syndrome and patients with thoracic aortic aneurysm using MRI (**Part II**). Finally, the association between morphological and functional vessel wall imaging parameters and end-organ damage was assessed by MRI (**Part III**).

PART I: IMAGING OF VESSEL MORPHOLOGY

A multi-contrast MRI protocol with a combination of five MRI sequences (T1, T2- and proton-density weighted (PD) gradient-echo and spin-echo) allows for morphological vessel wall imaging. For clinical application, a high reproducibility and high image quality is warranted. The aim of **Chapter 2** was to investigate the scan-rescan reproducibility together with intra- and inter-observer reproducibility of five MRI sequences; T1-TFE, T2-TSE, PD-TSE, T1-TSE and 3D TOF. Twenty healthy volunteers (55 % male, mean age=26yrs) underwent repeated MRI examinations (3T Philips MRI) of the left carotid artery vessel wall with the five MRI sequences. For scan-rescan reproducibility, intraclass correlation coefficients (ICC) were excellent for all sequences ranging from 0.79 to 0.95. The intra-observer ICC ranged from 0.89-0.98 and the inter-observer ICC ranged from 0.84-0.96, for both lumen and vessel wall assessment. This study demonstrated that by high field 3T MRI, vessel wall and lumen area of the carotid artery can be assessed with excellent scan-rescan, intra- and inter-observer reproducibility for all five MRI sequences.

In **Chapter 3** we described the development of ultra-high field 7T MRI hardware and protocols for vessel wall imaging of the carotid artery and we compared quantitative parameters of vessel wall morphology and image quality between 3T and 7T MRI. Eighteen volunteers (11 males, 7 females, mean age=29 ± 7 yrs) underwent MRI-examinations at 7T (using a custom built surface transmit/receive coil of 15 cm diameter) and at 3T (using a commercial phased-array coil with two flexible oval elements, each 14 x 17 cm). Morphologic carotid vessel wall measurements were comparable between 7T and 3T for both T1-weighted images (lumen area; ICC: 0.81, vessel wall area; ICC: 0.84) and T2-weighted images (lumen area; ICC: 0.97, vessel wall area; ICC: 0.92). At 7T, the signal-to-

noise ratio of the vessel wall (SNR_{vw}) and contrast-to-noise ratio (CNR) were significantly higher as compared to 3T MRI for both T1- ($p < 0.001$) and T2-weighted images ($P < 0.05$), with gain factors ranging from 1.3 to 3.6. This study demonstrated that ultra-high field 7T MRI carotid vessel wall imaging is feasible and that 7T MRI of the common carotid artery has comparable accuracy to 3T MRI for determining luminal area and vessel wall area.

Furthermore, 7-T MRI of the common carotid artery showed improved SNR_{vw} and CNR compared with 3-T MRI. Therefore, ultra-high field 7T vessel wall MRI may enable more detailed assessment of plaque morphology.

PART II: IMAGING OF VESSEL WALL FUNCTION

Aorta pulse wave velocity (PWV) assessment by velocity-encoded (VE) MRI allows for the quantification of aortic stiffness, a measure of vessel wall function. A higher PWV represents a stiffer aorta. The accuracy of PWV assessment as well as the scan time may be influenced by the spatial (i.e. number of sampling locations along the aorta) and temporal sampling density.

Chapter 4 evaluated the effect of spatial and temporal sampling density on aortic PWV assessment from VE-MRI in 23 patients with Marfan syndrome. Three PWV-methods were evaluated: (1) reference $PWV_{i.p.}$ from in-plane velocity-encoded MRI; (2) conventional $PWV_{t.p.}$ from through-plane velocity-encoded MRI at three aortic locations; (3) EPI-accelerated $PWV_{t.p.}$ with sparse temporal resolution at five aortic locations in 23 Marfan syndrome patients. In the total aorta, we found that despite inferior temporal resolution, EPI-accelerated $PWV_{t.p.}$ showed stronger correlation ($r = 0.92$ versus $r = 0.65$, $p = 0.03$) with reference $PWV_{i.p.}$ as compared to conventional $PWV_{t.p.}$. Of note, a 84% scan time reduction achieved for EPI-accelerated $PWV_{t.p.}$ when compared to conventional $PWV_{t.p.}$. In the aortic arch, correlation was comparable for both EPI-accelerated and conventional $PWV_{t.p.}$ with reference $PWV_{i.p.}$ ($r = 0.66$ versus $r = 0.67$, $p = 0.46$), albeit a 92% scan-time reduction by EPI-acceleration. This chapter showed that improving spatial sampling density by adding two acquisition planes along the aorta results in more accurate PWV-assessment even when temporal resolution decreases.

Chapter 5 assessed MRI-assessed regional pulse wave velocity for predicting absence of regional aorta luminal growth in 21 Marfan syndrome patients at 2 year follow-up. Regional PWV at baseline was increased in 17 out of 102 segments (17%). Significant luminal growth at follow-up was reported in 14 segments (14%). The specificity of regional PWV-testing for predicting absence of regional aortic luminal growth was $\geq 78\%$ for all aortic segments, sensitivity was $\leq 33\%$. This chapter showed that regional PWV was significantly increased in Marfan syndrome patients as compared to healthy volunteers within similar age range in all aortic segments except the ascending aorta. Furthermore,

1 regional PWV-assessment had moderate to high specificity for all aortic segments in
2 Marfan syndrome patients.

3
4 In analogy to Chapter 5, we aimed to investigate the coupling between regional PWV
5 and aortic luminal diameter in patients with thoracic aortic aneurysm in which the
6 Marfan syndrome was excluded. Regional aortic wall stiffness and luminal size are
7 considered to be coupled in patients with thoracic aortic aneurysm. In **Chapter 6** we
8 investigated the local aortic wall compliance measured by PWV in 40 patients with
9 thoracic aortic aneurysm and we evaluated coupling between regional PWV and aortic
10 luminal diameter in these patients. Mean diameter was 44 ± 5 mm for the aortic root and
11 39 ± 5 mm for the ascending aorta. PWV was increased compared to age-related normal
12 values in 36 (19%) aortic segments. Aortic diameter was increased in 28 (14%) segments.
13 Specificity was $\geq 84\%$ in the descending thoracic to abdominal aorta and $\geq 68\%$ in the
14 ascending-aorta and aortic arch. These findings indicate that normal PWV rules out
15 dilatation. In contrast, sensitivity was low, in particular in the ascending aorta and aortic
16 arch, indicating that regional PWV testing was marginal at detecting present disease.
17 This study provides information that in patients with thoracic aortic aneurysm, aortic
18 stiffness assessment can potentially provide complimentary prognostic value to the
19 monitoring of aortic diameter for disease progression, since intervention before aortic
20 dissection and/or rupture is paramount.

21
22 Next to aortic stiffness measurements, velocity-encoded MRI is a modality that poten-
23 tially enables wave propagation sampling along the carotid arterial trajectory from the
24 common carotid artery into the internal carotid artery. Accordingly, **Chapter 7** aimed
25 to explore the differences in arterial stiffness of the aorta and carotid artery, assessed
26 by PWV. Secondly, to evaluate the blood flow volume distribution towards the carotid
27 circulation and to assess the effect of aging on the coupling between aortic and carotid
28 PWV in 32 healthy volunteers. Volunteers were divided into adult younger volunteers
29 (age < 30 years, n = 16) and sixteen older volunteers (age > 45 years, n = 16). Both aortic and
30 carotid artery PWV were higher in older versus younger volunteers (aorta: mean PWV
31 7.4 ± 1.4 m/s versus 4.9 ± 0.7 m/s, $p < 0.001$; carotid artery: mean PWV 6.9 ± 1.5 m/s versus
32 5.7 ± 1.0 m/s, $p = 0.0015$). Aortic versus carotid PWV-ratio was 1.2 for younger volunteers
33 and 0.95 for older volunteers, demonstrating leveling of wall stiffness. Furthermore, the
34 flow volume per minute in the internal carotid artery, indexed for body surface area,
35 was significantly lower for older versus younger volunteers (mean volume 177 ± 42 ml/
36 min/m^2 versus 147 ± 32 ml/min/ m^2 , $p = 0.028$), whereas flow volumes in the aorta and
37 common carotid artery were not significantly different between groups. The fraction of
38 blood flow volume towards the brain was smaller for older versus younger volunteers
39 ($61 \pm 9\%$ versus $71 \pm 8\%$, $p = 0.002$). This study demonstrated the association between
40 PWV-leveling between aorta and carotid artery at older age with a reduction in blood
41 flow volume towards the brain.

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PART III: IMAGING OF VESSEL WALL MORPHOLOGY AND VESSEL WALL

FUNCTION

In **Chapter 8**, the association between vessel wall morphology and function in both the aorta and the carotid artery was evaluated in 32 healthy volunteers (mean age 41 ± 16 years). PWV and vessel wall area (VWA) were associated within the same vascular territory, whereas the association was less strong across vascular territories, both for the aorta ($r=0.71$, $p<0.0001$ for PWV_{aorta} and VWA_{aorta} versus $r=0.53$, $p=0.002$ for PWV_{aorta} and $VWA_{carotid\ artery}$, respectively) as well as for the carotid artery ($r=0.61$, $p<0.0001$ for $PWV_{carotid\ artery}$ and $VWA_{carotid\ artery}$ versus $r=0.46$, $p=0.008$ for $PWV_{carotid\ artery}$ and VWA_{aorta}). These results indicate that site-specific coupling exists between vessel wall thickness and function.

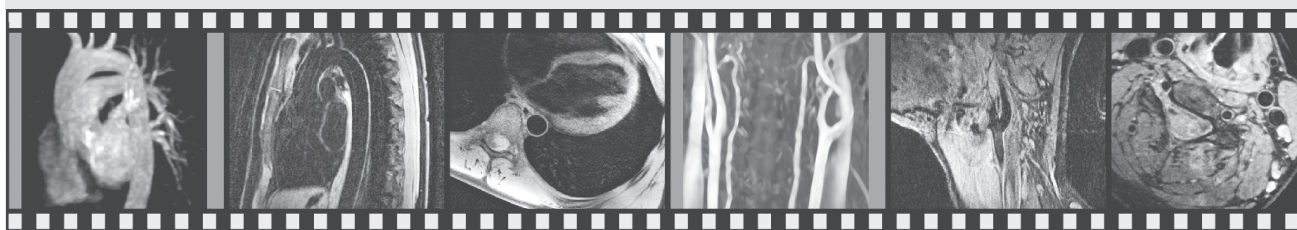
Chapter 9 reports on the association between carotid vessel wall imaging parameters and cerebral white matter lesions (WML) in 20 myocardial infarction patients. Significant correlation (Pearson $r=0.45$, $P=0.046$) between vessel wall thickness (VWT) and PWV was observed. Furthermore, in the group of patients with high VWT, the median WML score was significant higher as compared to the group without increased VWT (4.0 vs 3.0, $p=0.035$). This finding might indicate a link between carotid vessel wall thickness and cerebral small vessel disease in patients with established atherosclerotic disease.

CONCLUSIONS

This thesis evaluates morphological and functional vessel wall properties measured by MR imaging techniques in healthy volunteers and patients with various diseases (i.e. Marfan syndrome patients, patients with thoracic aortic aneurysm and patients with a previous myocardial infarction). This thesis shows that imaging of carotid vessel wall morphology can be reproducibly assessed by high-field MRI and that carotid vessel wall imaging benefits from imaging at higher field strengths. For a functional imaging parameter, the aorta PWV, improving spatial sampling density resulted in more accurate PWV-assessment, even when temporal resolution decreased. Moreover, a scan-time reduction was achieved. Aortic PWV showed a high specificity for predicting absence of regional aortic luminal growth for all aortic segments in Marfan syndrome patients. In patients with thoracic aortic aneurysm, regional PWV showed high specificity in the descending thoracic to abdominal aorta and moderate results in the ascending aorta and aortic arch. Next, PWV-leveling between aorta and carotid artery at older age was associated with a reduction in blood flow volume towards the brain. Furthermore, vessel wall morphology and function were associated in healthy volunteers and in patients with established atherosclerotic disease. Finally, our findings might indicate a link between atherosclerotic large vessel disease and cerebral small vessel disease in patients with established atherosclerotic disease.

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SAMENVATTING EN CONCLUSIES



SAMENVATTING

Het doel van het onderzoek beschreven in dit proefschrift was om de morfologie en de functie van de arteriële vaatwand in beeld te brengen in vrijwilligers en verschillende patiëntenpopulaties met behulp van technieken gebaseerd op Magnetische Resonantie Imaging (MRI). De algemene inleiding (**Hoofdstuk 1**) van dit proefschrift geeft achtergrondinformatie over morfologische (i.e. vaatwandverdikking) en functionele (i.e. verstijving) veranderingen van de vaatwand die een belangrijke rol spelen bij de ontwikkeling van hart- en vaatziekten. De mogelijkheden van MRI om zowel de morfologie (i.e. dikte) als de functie (i.e. elasticiteit) van de vaatwand in verschillende arteriële vaatgebieden in beeld te brengen, worden toegelicht.

In **Deel I** (hoofdstukken 2 en 3) wordt de beeldvorming van de morfologie van de vaatwand met MRI geëvalueerd. In **Deel II** (hoofdstukken 4 tot en met 7) wordt de beeldvorming van de functie van de vaatwand en de voorspellende waarde hiervan bij patiënten met het Marfan syndroom en patiënten met een aneurysma van de thoracale aorta onderzocht met MRI. Tevens wordt een MRI methode geïntroduceerd waarmee bij vrijwilligers de functie van de vaatwand van de halsslagader wordt vergeleken met de functie van de vaatwand in de aortaboog. Tot slot wordt in **Deel III** (hoofdstukken 8 en 9) het verband tussen de morfologie en de functie van de vaatwand en eind-orgaanschade geëvalueerd met behulp van MRI.

DEEL I: BEELDVORMING VAN DE MORFOLOGIE VAN DE VAATWAND

Een MRI protocol, bestaande uit een combinatie van vijf verschillende MRI sequenties met verschillende contrast-wegingen, maakt beeldvorming van de morfologie van de vaatwand mogelijk. Voor klinische toepassing is een hoge reproduceerbaarheid en goede beeldkwaliteit noodzakelijk.

Het doel van de studie beschreven in **Hoofdstuk 2** was om de reproduceerbaarheid van het MRI protocol door middel van een zogenaamde scan-rescan studie en de evaluatie van intra- en inter-observer analyse te onderzoeken. Twintig gezonde vrijwilligers (1155% mannen, gemiddelde leeftijd 26 jaar) ondergingen herhaalde onderzoeken op een 3T MRI scanner waarbij de vaatwand van de linkerhalsslagader (arteria carotis) met behulp van vijf MRI sequenties met verschillende contrast-weging in beeld werd gebracht. De scan-rescan reproduceerbaarheid, uitgedrukt in intra-class correlatiecoëfficiënten (ICC), was uitstekend voor alle sequenties, met ICC variërend tussen 0.79 en 0.95. De intra-observer ICC varieerde tussen 0.89 en 0.98 en de inter-observer ICC varieerde tussen 0.84 en 0.96, zowel voor de bepaling van het lumen als van de vaatwand. Dit onderzoek liet zien dat door middel van beeldvorming met hoge MRI veldsterkte zowel de vaatwand als het lumen met uitstekende scan-rescan, intra- and inter-observer reproduceerbaarheid voor vijf MRI sequenties met verschillende contrast-weging kan worden vastgesteld.

In **Hoofdstuk 3** worden de ontwikkelingen beschreven die we voor de beeldvorming op een ultra-hoog 7Tesla (7T) MRI systeem hebben bereikt, zowel op het gebied van hardware als acquisitieprotocollen voor de beeldvorming van de vaatwand van de arteria carotis. In een studie bij achttien vrijwilligers hebben we kwantitatieve parameters voor vaatwandmorfologie van de arterie en beeldkwaliteit tussen 3T en 7T MRI vergeleken. Bij de 7T MRI-onderzoeken werd gebruik gemaakt van een aangepaste oppervlakte zend/ontvangstspoel terwijl voor het 3T MRI onderzoek gebruik werd gemaakt van een commerciële oppervlakte ontvangstspoel. De morfologie van de vaatwand van de arteria carotis was goed vergelijkbaar wanneer deze in beeld werd gebracht met ultrahoog (7T) en hoog (3T) MRI veldsterkte. Dit gold zowel de T1-gewogen afbeeldingen (lumen ICC: 0.81, vaatwand ICC: 0.84) als de T2-gewogen afbeeldingen (lumen ICC: 0.97, vaatwand ICC: 0.92). De signaal-ruis verhouding gemeten in de vaatwand en de contrast-ruis verhouding tussen vaatwand en omringend weefsel bleek significant hoger te zijn in beelden verkregen met 7T dan in beelden verkregen met 3T MRI, en dit gold voor zowel de T1-gewogen afbeeldingen ($p < 0.001$) als de T2-gewogen afbeeldingen ($p < 0.05$), met toename coëfficiënten variërend van 1.3 tot 3.6. Dit onderzoek liet zien dat met ultrahoog 7T MRI beeldvorming van de carotis vaatwand uitvoerbaar is en metingen aan de vaatwand en het lumen van de arteria carotis communis waren voor 7T MRI beelden vergelijkbaar nauwkeurig als 3T MRI beelden. Bovendien had 7T MRI een betere signaal-ruis verhouding en contrast-ruis verhouding dan 3T MRI. Daarom is ultra-hoog 7T MRI van de vaatwand mogelijk in staat om de plaquemorfologie meer gedetailleerd af te beelden.

DEEL II: BEELDVORMING VAN DE FUNCTIE VAN DE VAATWAND

De functie van de vaatwand kan worden uitgedrukt in een maat voor vaatwandstijfheid. Er zijn verschillende maten in gebruik die stijfheid direct of indirect beschrijven. Een veel-gebruikte maat die indirect de vaatwandstijfheid van de aorta beschrijft is de pulsgolfsnelheid (PWV), de voortplantingssnelheid van de systolische drukgolf of flowgolf door de aorta. Met behulp van snelheidsgecodeerde MRI kan deze golfsnelheid gemeten worden. PWV is een indirecte maat voor de elasticiteit van de aortavaatwand: een hogere PWV geeft een stijvere aorta weer.

De nauwkeurigheid van de bepaling van de vaatwandstijfheid worden mogelijk beïnvloed door de spatiële resolutie (het aantal acquisitielocaties ten opzichte van de aorta) en de temporele resolutie van de MRI acquisitie.

In **Hoofdstuk 4** werd de invloed van de spatiële en temporele resolutie op de nauwkeurigheid van de bepaling van de vaatwandstijfheid van de aorta nagegaan bij 23 Marfan syndroom patiënten. We hebben drie methoden om de PWV in de aorta met snelheidsgecodeerde MRI vast te leggen, met elkaar vergeleken. Allereerst is de PWV nauwkeurig gemeten door de aorta in zijn geheel in drie vlakken in beeld te brengen

en de bloedsnelheid in twee richtingen in het vlak te coderen. Deze beschrijving van de PWV gebruiken we als referentiestandaard; vervolgens is de PWV op de meest gangbare manier vastgelegd, door middel van drie opnames die loodrecht op de aorta gepland zijn en codering van de bloedsnelheid loodrecht op deze vlakken; tenslotte is een versnelde MRI techniek gebruikt, waarbij een verminderde temporele resolutie verkregen wordt maar door de beschikbare tijds winst meer meetvlakken langs de aorta kunnen worden geplaatst en de samplingsdichtheid omhoog gaat. De toepassing van deze versnelde MRI techniek met vijf meetvlakken langs de aorta correleerde wat betreft PWV-bepaling voor de gehele aorta sterker met de referentiestandaard dan de conventionele methode met drie meetvlakken en een hogere temporele resolutie ($r=0.92$ versus $r=0.65$, $p=0.03$). De winst in acquisitietijd met deze versnelde aanpak was 84% ten opzichte van de conventionele aanpak. Voor PWV-bepaling in enkel de aortaboog was de correlatie voor beide technieken met de referentiestandaard vergelijkbaar ($r=0.66$ versus $r=0.67$, $p=0.46$), hoewel winst in acquisitietijd met de versnelde MRI-techniek 92% was ten opzichte van de conventionele methode. In dit hoofdstuk hebben we laten zien dat het verhogen van de samplingsdichtheid door middel van het toevoegen van meetvlakken langs de aorta resulteert in een hogere nauwkeurigheid in PWV- bepaling ondanks een lagere temporele resolutie.

In **Hoofdstuk 5** wordt de voorspellende waarde van MRI-bepaalde regionale aortavaatwandstijfheid voor het uitblijven van lumengroei beschreven door middel van een studie die is uitgevoerd bij 21 patiënten met het Marfan syndroom. De patiënten zijn 2 jaar gevolgd. De vaatwandstijfheid van de regionale aorta gemeten bij aanvang van de studie bleek verhoogd te zijn ten opzichte van bekende normaalwaarden in 17 van de 102 geanalyseerde aortasegmenten (17%). In 14 segmenten (14%) werd na 2 jaar follow-up significante lumengroei gezien. De specificiteit van de regionale aortavaatwandstijfheidbepaling voor het voorspellen van het uitblijven van regionale lumengroei was $\geq 78\%$ voor alle aortasegmenten; de sensitiviteit bedroeg $\leq 33\%$. In dit hoofdstuk hebben we aangetoond aan dat de regionale aortavaatwandstijfheid in alle segmenten van de aorta significant verhoogd was bij patiënten met het Marfan syndroom vergeleken met gezonde vrijwilligers binnen dezelfde leeftijdsrange. Alleen voor de ascenderende aorta kon dit niet worden aangetoond. De bepaling van de regionale aortavaatwandstijfheid liet een redelijk tot hoge specificiteit zien voor het voorspellen van het uitblijven van lumengroei over twee jaar bij patiënten met het Marfan syndroom.

Op een vergelijkbare wijze als beschreven in Hoofdstuk 5 hebben we bij patiënten met een aneurysma van de thoracale aorta de relatie tussen de regionale aortavaatwandstijfheid en de diameter van het lumen van de aorta onderzocht. In **Hoofdstuk 6** zijn de resultaten beschreven die we bij een studie uitgevoerd met 40 patiënten hebben verkregen. De gemiddelde diameter van de aortawortel was 44 ± 5 mm en 39 ± 5 mm voor de ascenderende aorta. De regionale vaatwandstijfheid van de aorta was verhoogd vergeleken met leeftijd-gerelateerde normaalwaarden in 36 (19%) aortasegmenten. De

1 aortadiameter was vergroot in 28 (14%) segmenten. De specificiteit van de regionale
2 PWV-bepaling voor detectie van een niet-vergrote aortadiameter bedroeg $\geq 84\%$ voor
3 het descenderende deel van de thoracale en abdominale aorta en $\geq 66\%$ voor de ascen-
4 derende aorta en de aortaboog.

5
6 Beide hoofdstukken liet zien dat bij patiënten met het Marfan syndroom of een aneu-
7 rysma van de thoracale aorta, een bepaling van de regionale aortavaatwandstijfheid,
8 naast het vervolgen van de aortadiameter, mogelijk een toegevoegde prognostische
9 waarde heeft voor het evalueren van de progressie van ziekte. Dit kan klinisch nuttig zijn
10 daar tijdige interventie voordat aortadissectie optreedt van essentieel belang is.

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12 Vergelijkbaar aan de PWV-bepaling in de aorta, waarmee de vaatwandstijfheid be-
13 schreven wordt, kan de propagatiesnelheid van de systolische flowgolf en daarmee de
14 PWV in de arteria carotis over het traject vanaf de communis tot bovenin de interna
15 met snelheidsgecodeerde MRI bepaald worden. Het doel van de studie beschreven in
16 **Hoofdstuk 7** was om de verschillen in vaatwandstijfheid tussen de aortaboog en de ar-
17 teria carotis en het effect van de leeftijd hierop onderzoeken. Hiervoor zijn 32 gezonde
18 vrijwilligers met MRI onderzocht en de verschillen in PWV tussen de aortaboog en de
19 arteria carotis werd gerelateerd aan de bloedtoevoer door de arteria carotis. De vrijwil-
20 ligers werden verdeeld in twee groepen: een groep van 16 volwassen jonge vrijwilligers
21 (leeftijd < 30 jaar) en 16 oudere vrijwilligers (leeftijd > 45 jaar). Zowel de vaatwandstijfheid
22 van de aorta als die van de arteria carotis was hoger bij de oudere vrijwilligers dan bij de
23 jongere vrijwilligers (aorta: 7.4 ± 1.4 m/s versus 4.9 ± 0.7 m/s, $p < 0.001$; carotis: 6.9 ± 1.5 m/s
24 versus 5.7 ± 1.0 m/s, $p = 0.0015$). De verhouding in PWV van de aorta en de arteria carotis
25 was 1.2 voor de jongere vrijwilligers en 0.95 voor de oudere vrijwilligers, wat duidt op
26 een matching van de vaatwandstijfheid tussen beide vaatgebieden bij oudere leeftijd.
27 De bloedtoevoer in de arteria carotis interna, geïndexeerd voor body surface area, was
28 significant lager bij de oudere vrijwilligers dan bij de jongere vrijwilligers (respectievelijk
29 177 ± 42 ml/min/m² versus 147 ± 32 ml/min/m², $p = 0.028$). De bloedvolumina gemeten in
30 zowel de aorta als de arteria carotis communis verschilden niet tussen de beide leef-
31 tijdsgroepen. De fractie bloedtoevoer naar de cerebrale circulatie was kleiner bij de
32 oudere vrijwilligers dan bij de jongere vrijwilligers ($61 \pm 9\%$ versus $71 \pm 8\%$, $p = 0.002$).
33 Deze resultaten laten zien dat er bij oudere vrijwilligers een verband bestaat tussen de
34 matching van vaatwandstijfheid in de aorta en de arteria carotis en een verminderde
35 bloedtoevoer naar de cerebrale circulatie.

DEEL III: BEELDVORMING VAN DE MORFOLOGIE EN FUNCTIE VAN DE

VAATWAND

In **Hoofdstuk 8** werd het verband onderzocht tussen de met MRI bepaalde vaatwandstijfheid en vaatwandverdikking in de aorta en de arteria carotis bij 32 gezonde vrijwilligers (leeftijd 41 ± 16 jaar). Het verband tussen vaatwandstijfheid en vaatwandverdikking was sterker wanneer beide gemeten werden in hetzelfde vaatgebied, dan wanneer beide gemeten werden in verschillende vaatgebieden.

Hoofdstuk 9 rapporteert het verband tussen de vaatwand van de arteria carotis en afwijkingen gemeten in de cerebrale witte stof. Deze studie is uitgevoerd bij 20 patiënten die een myocardinfarct hadden ondergaan. Een significante correlatie (Pearson $r=0.45$, $p=0.046$) werd waargenomen tussen de vaatwanddikte en de vaatwandstijfheid van de arteria carotis. Tevens werd er bij patiënten met een grotere vaatwanddikte een significant grotere aantal afwijkingen in de cerebrale witte stof waargenomen dan bij patiënten met een kleinere vaatwanddikte (4.0 versus 3.0, $p=0.035$). Deze bevinding impliceert een mogelijk verband tussen atherosclerotische veranderingen in de grote vaten en cerebrale vaatschade.

CONCLUSIES

Dit proefschrift beschrijft de bepaling van, en de onderlinge relatie tussen, morfologische en functionele vaatwandparameters, in beeld gebracht middels MRI, bij gezonde vrijwilligers en bij verschillende patiënten (patiënten met het Marfan syndroom, patiënten met een aneurysma van de thoracale aorta en patiënten die een myocardinfarct hebben ondergaan). Uit de beschreven onderzoeken bleek dat morfologische vaatwandparameters van de arteria carotis met een goede reproduceerbaarheid gemeten kunnen worden in beelden die verkregen zijn met behulp van 3T MRI en dat de beeldvorming van de vaatwand van de arteria carotis duidelijk baat heeft bij een hogere magneetveldsterkte (7T).

Voor de bepaling van een functionele vaatwandparameter, de aorta PWV, bleek het verhogen van de samplingsdichtheid langs de aorta te resulteren in een hogere nauwkeurigheid, ondanks dat hierbij een lagere temporele resolutie beschikbaar was. Tevens was er via deze methode een substantiële winst in acquisitietijd.

Bij patiënten met het Marfan syndroom bleek de bepaling van de regionale aortavaatwandstijfheid een hoge specificiteit te bezitten wanneer deze gebruikt wordt voor het voorspellen van het uitblijven van regionale aortadilatatie. Bij patiënten met een aneurysma van de thoracale aorta had de bepaling van de regionale aortavaatwandstijfheid een hoge specificiteit in detectie van uitblijvende dilatatie in de descenderende

1 thoracale aorta en de abdominale aorta, maar slechts een matige specificiteit in de
2 ascenderende aorta en de aortaboog.

3 Voorts werd een verband vastgesteld tussen de matching van de vaatwandstijfheid in
4 de aortaboog en de arteria carotis en de verminderde bloedtoevoer naar de hersenen
5 bij oudere vrijwilligers.

6 De morfologie en functie van de vaatwand zijn sterk aan elkaar gerelateerd wanneer
7 deze in hetzelfde vaatgebied gemeten worden, en dat gold voor zowel vrijwilligers als
8 patiënten. Tenslotte impliceren onze bevindingen een mogelijk verband tussen athero-
9 sclerotische veranderingen in de grote vaten en cerebrale vaatschade bij patiënten met
10 aangetoonde atherosclerose.

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LIST OF PUBLICATIONS

Papers

Kröner ESJ, van Velzen JE, Boogers MJ, Siebelink HM, Schalij MJ, Kroft LJ, de Roos A, van der Wall EE, Jukema JW, Reiber JH, Schuijf JD, Bax JJ. Positive remodeling on coronary computed tomography as a marker for plaque vulnerability on virtual histology intravascular ultrasound. *Am J Cardiol* 2011;107:1725-9.

Van der Wall EE, **Kröner ESJ**, Siebelink HM, Scholte AJ, Schalij MJ. Does heart rate influence CMR image quality of the coronary vessel wall? *Int J Cardiovasc Imaging* 2012;28:563-5.

Kröner ESJ, van der Geest RJ, Scholte AJ, Kroft LJ, van den Boogaard PJ, Hendriksen D, Lamb HJ, Siebelink HM, Mulder BJ, Groenink M, Radonic T, Hilhorst-Hofstee Y, Bax JJ, van der Wall EE, de Roos A, Reiber JH, Westenberg JJ. Evaluation of sampling density on the accuracy of aortic pulse wave velocity from velocity-encoded MRI in patients with Marfan syndrome. *J Magn Reson Imaging* 2012;36:1470-6.

Kröner ESJ, van Schinkel LD, Versluis MJ, Brouwer NJ, van den Boogaard PJ, van der Wall EE, de Roos A, Webb AG, Siebelink HM, Lamb HJ. Ultrahigh-field 7-T magnetic resonance carotid vessel wall imaging: initial experience in comparison with 3-T field strength. *Invest Radiol* 2012;47:697-704.

Kröner ESJ, Scholte AJ, de Koning PJ, van den Boogaard PJ, Kroft LJ, van der Geest RJ, Hilhorst-Hofstee Y, Lamb HJ, Siebelink HM, Mulder BJ, Groenink M, Radonic T, van der Wall EE, de Roos A, Reiber JH, Westenberg JJ. MRI-assessed regional pulse wave velocity for predicting absence of regional aorta luminal growth in marfan syndrome. *Int J Cardiol* 2013;167:2977-82.

Kröner ESJ, Lamb HJ, Siebelink HM, Putter H, van der Geest RJ, van der Wall EE, de Roos A, Westenberg JJ. Coupling of vessel wall morphology and function in the aorta and the carotid artery: an evaluation with MRI. *Int J Cardiovasc Imaging*. 2014;30:91-8.

Kröner ESJ, Lamb HJ, Siebelink HM, Cannegieter SC, van den Boogaard PJ, van der Wall EE, de Roos A, Westenberg JJ. Pulse wave velocity and flow in the carotid artery versus the aortic arch: effects of aging. *J Magn Reson Imaging* 2014;40:287-93.

Kröner ESJ, Westenberg JJ, Kroft LJM, Brouwer NJ, van den Boogaard PJ, Scholte AJHA. Coupling between MRI-assessed regional aortic pulse wave velocity and diameters in patients with thoracic aortic aneurysm. *Neth Heart J* 2015; in press

Kröner ESJ, van der Grond J, Westenberg JJM, van der Wall EE, Siebelink HJ, Lamb HJ. Morphological and functional carotid vessel wall properties in relation to cerebral white matter lesions in myocardial infarction patients. *Neth Heart J* 2015; in press

Oral and poster presentations

Positive remodeling on coronary computed tomography as a marker for plaque vulnerability on virtual histology intravascular ultrasound. (poster presentation)
American College of Cardiology, 2011, New Orleans, USA; European Society of Cardiology, 2011, Paris, The Netherlands; Netherlands Society of Cardiology, 2010, Arnhem, The Netherlands;

Evaluation of sampling density on the accuracy of aortic pulse wave velocity from velocity-encoded magnetic resonance imaging in patients with marfan syndrome.
American Heart Association, 2011, Orlando, USA; European Society of Cardiac Radiology, 2011, Amsterdam, The Netherlands; Netherlands Society of Cardiology, 2011, Arnhem, The Netherlands; Society of Cardiovascular Magnetic Resonance, 2011, Nice, France.

MRI-assessed pulse wave velocity for predicting aorta luminal growth in marfan syndrome. (poster presentation)
Society of Cardiovascular Magnetic Resonance, 2012, Orlando, USA; European Society of Cardiology, 2012, München, Germany.

High field carotid vessel wall imaging; scan-rescan reproducibility of five MR-weightings.
Society of Cardiovascular Magnetic Resonance, 2011, Nice, France;

High field carotid vessel wall imaging: a study on reproducibility. (poster presentation)
American College of Cardiology, 2011, New Orleans, USA; European Society of Cardiology, 2011, Paris, France.

Aorta Physiology: the role of MRI
CVOI Imaging course, 2011, Utrecht, the Netherlands

Ultra high field 7T MR Carotid Vessel Wall Imaging: comparison with 3T. (poster presentation)
American Heart Association, 2012, Chicago, USA; Netherlands Society of Cardiology, 2012, Noordwijkerhout, The Netherlands; European Society of Cardiology, 2012, Munchen, Germany.

Pulse Wave Velocity and Flow in the Carotid Artery versus the Aortic Arch: Effects of Aging.
European Society of Cardiac Radiology, 2012, Barcelona, Spain

Pulsatility and pulse wave velocity in the carotid artery: assessment with high-field velocity-encoded MRI. (poster presentation)
American Heart Association, 2012, Chicago, USA and European Society of Cardiology, 2012, Muchen, Germany.

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CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 26 april 1985 in Rotterdam. In 2003 behaalde zij haar eindexamen aan het Erasmiaans Gymnasium te Rotterdam. Zij ving in hetzelfde jaar aan met de studie Geneeskunde aan de Universiteit Leiden. Tijdens haar studie heeft zij een klinische stage (KNO) gelopen in het Hôpital Lariboisière (Parijs, Frankrijk) en heeft zij onderzoek gedaan bij het Centre voor Cardiovascular Science aan de Universiteit van Edinburgh (Edinburgh, Schotland). In 2010 haalde zij haar arts-examen, waarna zij direct startte in het Leids Universitair Medisch Centrum met haar promotieonderzoek onder leiding van Prof. dr. E.E. van der Wall en Prof. dr. H.J. Lamb. De resultaten hiervan staan beschreven in dit proefschrift.

Per 1 mei 2013 is zij begonnen met haar opleiding tot cardioloog vanuit het Leids Universitair Medisch Centrum (opleider: Prof. Dr. M.J. Schalij). Recent heeft zij haar vooropleiding Interne Geneeskunde in het Bronovo Ziekenhuis te Den Haag (opleider: Dr. Y.W.J. Sijpkens) afgerond. De rest van haar opleiding tot cardioloog zal worden voortgezet in het Groene Hart Ziekenhuis te Gouda (opleider: Dr. M.W.J. van Hessen) en in het Leids Universitair Medisch Centrum.