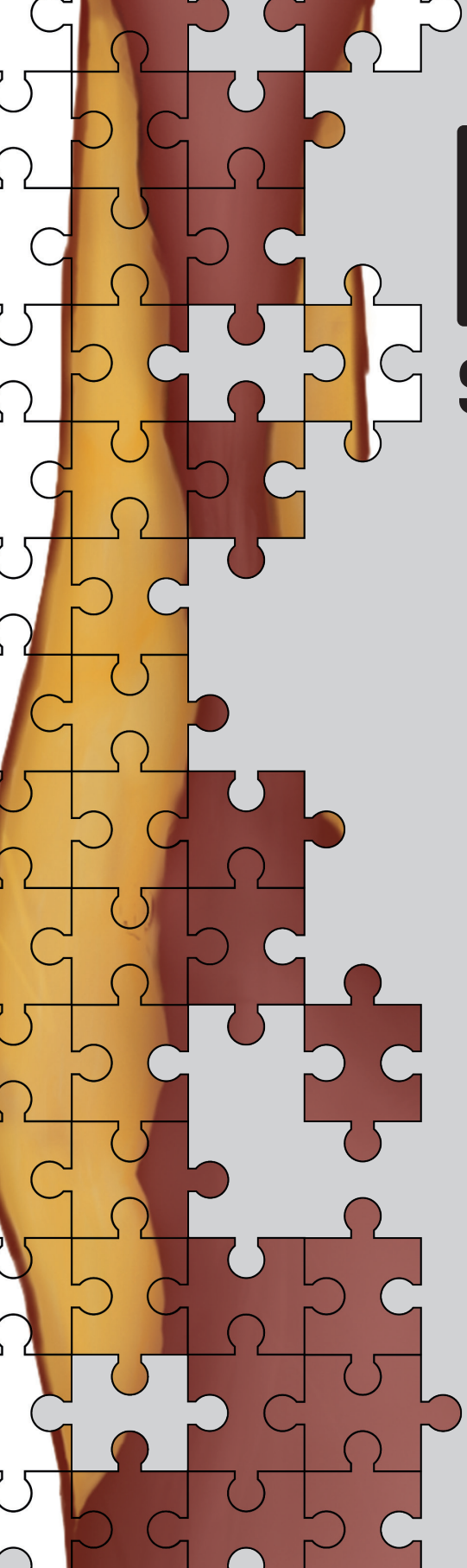
Dynamic contrast-enhanced MR imaging of artherosclerotic plaque microvasculature



Summary

Summary

Stroke is a large, health problem accounting for five million deaths and an additional five million disabled patients annually worldwide (1). In The Netherlands, stroke accounts for 21% of all cardiovascular deaths, with a total number of nearly 10.000 deaths in 2014 (2). Ischemic strokes, in which blood supply to (part of) the brain is (temporarily) impaired, are responsible for almost 90% of the strokes, with hemorrhagic strokes accounting for the remaining 10% (3). Of the ischemic strokes, 15-20% are caused by atherosclerosis of the carotid artery (4).

In atherosclerosis, infiltration of macrophages and build up of fatty deposits and scar tissue leads to a local thickening of the vessel wall. Current guidelines for the treatment of patients with an atherosclerotic plaque in the carotid artery are based on the results of large randomized surgical trials performed in the early 90s. These trials have shown that symptomatic patients with a stenosis of 70-99% that have experienced a recent cerebrovascular ischemic event benefit from carotid endartorectomy (CEA) with a number needed to treat (NNT) of 6. For symptomatic patients with a 50-69% stenosis the NNT increases to 22, making CEA only marginally effective (5). During CEA, the vascular surgeon surgically removes the carotid artery plaque. Additionally, male patients with a carotid stenosis ≥50 % who have experienced a recent ischemic event within two weeks are also eligible for CEA (6). Next to a CEA, symptomatic patients receive best medical treatment, consisting of anti-platelet therapy and cholesterol synthesis inhibitors (6).

Numerous histopathological studies performed on CEA specimen have shown that specific plaque characteristics are associated with an increased stroke incidence in symptomatic patients compared to asymptomatic patients (7-11). These “vulnerable plaques” are characterized by a large lipid-rich necrotic core (LRNC) with a thin fibrous cap, presence of inflammatory cells, ulcerations, and intraplaque hemorrhage (IPH) (12), while the presence of fibrous tissue is considered a stabilizing feature (13). Next to these plaque features, increased microvasculature of the atherosclerotic plaque has been suggested to be a characteristic of plaque vulnerability (14). In physiological conditions, microvessels are already present in the outer layer of the vessel wall, the adventitia. However, in atherosclerosis, microvessels grow from the adventitia into the plaque tissue as a result of angiogenic stimuli. These newly formed microvessels generally have a low integrity of the endothelium (15), providing a point of entry for inflammatory cells and erythrocytes. According to the fatigue hypothesis (16,17), ruptured microvessels may also be the result of the biomechanical load on the atherosclerotic vessel wall due to exposure to the arterial pressure wave during each heart beat. These repetitive deformations of the atherosclerotic plaque may result in minor tissue damage, accumulating over time into larger tissue damage (crack propagation).

Non-invasive imaging techniques of the atherosclerotic vessel wall may provide opportunities for improved patient stratification. Firstly, vessel wall imaging enables more accurate determination of outward remodeling of the vessel wall compared to angiographic techniques, in which only the vessel lumen is displayed. Secondly, vessel wall imaging enables in vivo visualization of plaque characteristics. Interest in the potential benefit of patient stratification based on (a number of) these vulnerable plaque characteristics has greatly increased over the past de-

cade, mainly owing to technical improvements of non-invasive imaging modalities. Moreover, since patients with a mild to moderate carotid stenosis rarely undergo CEA and the adventitial region of the vascular wall remains in situ after CEA, non-invasive imaging techniques enable an increased number of possibilities to study the role of vulnerable plaque characteristics over time. In particular patients with a mild to moderate stenosis may benefit from increased personalized treatment since for this patient population CEA is only marginally effective.

Non-invasive imaging and quantification of the plaque microvasculature can be performed using pharmacokinetic modeling of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) (18-24). Recent studies showed a weak link between increased plaque microvasculature and plaque inflammation (25,26) and the presence of intraplaque hemorrhage (27). However, it was shown that the correlation between plaque inflammation and microvasculature differs between symptomatic and asymptomatic plaques (26). Therefore, in vivo visualization of plaque microvasculature may not only provide further insight into pathological mechanisms involved in plaque development and destabilization, but may also provide additional information compared to other vulnerable plaque features.

The hypothesis of the present thesis is that non-invasive imaging of the plaque microvasculature with DCE-MRI can aid to gain further insight in the atherosclerotic process. To investigate this hypothesis, the following objectives are addressed in the present thesis:

- To further improve and validate DCE-MRI methodology
- To investigate the association between plaque microvasculature and important features of plaque vulnerability (plaque inflammation and presence of intraplaque hemorrhage)
- To explore whether plaque microvasculature is related to the type of cerebrovascular symptoms in patients with mild to moderate carotid stenosis
- To evaluate if DCE-MRI can be used as evaluation tool to investigate the effect of a heart-rate reducing therapy on features of plaque vulnerability

In chapter 2, an overview of the current state of DCE-MRI in the evaluation of plaque microvasculature in clinical and preclinical settings is provided. First, principles and acquisition methods of DCE-MRI and methods for (semi-)quantitative analysis of DCE-MRI data are discussed. Secondly, an overview is given of publications in which DCE-MRI of plaque microvasculature is applied. The main findings are summarized on the following aspects 1) the association of other plaque features with plaque microvasculature; 2) changes in plaque microvasculature over time; 3) comparison of different experimental animal groups and human subjects with a different cardiovascular risk profile; and 4) evaluation of the response to therapeutic interventions.

Accurate determination of the luminal contrast medium (CM) concentration (known as the vascular input function, VIF) is an essential requirement for quantitative analysis of DCE-MRI using pharmacokinetic modeling. In chapter 3, an alternative method for determination of the luminal CM concentration in DCE-MRI of the plaque microvasculature is introduced. This alternative method, based on the phase MRI signal, is compared to the currently commonly

employed method based on the magnitude MRI signal. The results from this chapter show that the magnitude-based VIF is strongly influenced by local blood velocity, leading to an underestimation of the CM concentration in the vessel lumen. Analysis of the model parameters determined from both methods show a moderate to strong correlation between the two methods, although absolute values differ significantly. Based on the results of this chapter, it is advised to use a phase-based VIF for quantification of DCE-MRI data of carotid plaques.

The relationship between atherosclerotic plaque microvasculature and other features of plaque vulnerability has been studied in a number of DCE-MRI studies. However, these studies have focused on a single region of the vascular wall, i.e. either the entire vessel wall or the outer layer of the vessel wall only. Therefore, the interchangeability of these results is not clear. The aim of the study described in chapter 4 is 1) to assess parameter agreement of K^{trans} between the two vascular regions and 2) to study the correlation with microvessel density on histology. The results from this study showed similar moderately strong correlations with plaque microvessel density on histology, though a significantly higher median K^{trans} was found in the adventitia compared to the entire vessel wall. These results suggest that both vascular regions reflect plaque microvessel density, though care should be taken when comparing absolute values between studies that assessed different regions.

A previous DCE-MRI study in 27 patients has shown a positive association between adventitial K^{trans} and the presence of IPH within carotid plaque (27). In chapter 5, the results of a study are presented with the aim to confirm the potential positive association between the plaque microvasculature and presence of IPH in a large cohort imaging study of 101 patients with carotid plaque. In this chapter, no difference in adventitial K^{trans} for patients with and without IPH is found, while a decreased vessel wall K^{trans} is found in patients with IPH. Therefore the positive association between plaque microvasculature and presence of IPH that was previously reported could not be confirmed in this chapter. The results of this chapter suggest that not only plaque microvasculature, but additional factors, such as a disrupted plaque surface, contribute to the development of IPH in carotid atherosclerosis. Several studies have already shown an important role for inflammation in the atherosclerotic process (28), which can be quantified using ^{18}F-FDG PET (29-31). It is generally believed that activated macrophages lead to the formation of new microvessels. Therefore, plaque inflammation and plaque microvasculature may be linked to each other. In chapter 6, the interchangeability of DCE-MRI and ^{18}F-FDG PET-CT is investigated in symptomatic patients with a mild carotid stenosis. In this chapter, a weak correlation coefficient (ρ=0.30, $p<0.05$) between the two imaging modalities was found, showing that both imaging methods are related to each other. These results indicate that both modalities are not interchangeable and the relationship between plaque inflammation and (development of) plaque microvasculature may be time-dependent.

It is known from previous studies that patients with a recent ischemic stroke have a higher risk of recurrent stroke compared to (ocular) transient ischemic attack (TIA) patients. The purpose of the cross-sectional study described in chapter 7 is to explore the association between plaque microvasculature with type of recent cerebrovascular events in symptomatic

patients with mild-to-moderate carotid stenosis. The results of this chapter show that the 75th percentile adventitial K^{trans} is significantly associated with a recent ischemic stroke compared to (ocular) TIA in multivariate analysis, independent of clinical risk factors. These results indicate a positive association of leaky plaque microvasculature with a recent ischemic stroke compared to (ocular) TIA. Future prospective longitudinal studies are needed to further investigate whether K^{trans} may serve as an imaging marker to predict (the type of) future cerebrovascular events.

Epidemiologic studies have shown that patients with an elevated resting heart rate have a lower life expectancy (32-34), independent of other risk factors. An increased heart rate may result in minor repetitive tissue damages within the vessel wall. Accumulation over time may result in larger tissue damage (crack propagation), such as microvessel rupture, cap fissures, and ultimately, cap rupture, leading to further progression of atherosclerosis. Chapter 8 describes the results of a preclinical rabbit study in which the effect of a heart-rate reducing agent on features of atherosclerotic plaque vulnerability is investigated. To investigate the role of heart rate, atherosclerosis was induced in New Zealand White Rabbits by a combination of a cholesterol-enriched diet and balloon injury of the abdominal aorta and heart-rate reduction was achieved by administration of Ivabradine. Results of this study show that heart-rate reducing therapy is associated with a reduction in vulnerable plaque features. A decrease of macrophage content on histology was found. Analysis of DCE-MRI and the microvessel density on histological specimens together suggest a reduction of the plaque microvasculature leakiness, but not the microvessel density itself. Therefore, this chapter suggests that heart-rate reduction may be a potential target for plaque stabilization.

In chapter 9, the results of the present thesis are put into perspective of the current literature. Additionally, this chapter elaborates about possible future perspectives of DCE-MRI.

In conclusion, the results of this thesis show that non-invasive imaging of the plaque microvasculature with DCE-MRI is an important tool to gain further insight in the role of plaque microvasculature in the atherosclerotic process, contributing to the in depth understanding of the pathophysiology of atherosclerosis.

References

1. Mackay J, Mensah G. The Atlas of Heart Disease and Stroke - Global Burden of Stroke. 2004.
2. Van Dis I, Buddeke J, Vaartjes I, Visseren FLJ, Bots ML. Hart- En Vaatziekten in Nederland 2015, Cijfers over Heden, Verleden En Toekomst. Hartstichting 2015.
3. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M et al. Heart Disease and Stroke Statistics-2016 Update: A Report from the American Heart Association. Circulation 2015;10.1161/CIR.0000000000000350.
4. Chaturvedi S, Bruno A, Feasby T, Holloway R, Benavente O, Cohen SN et al. Carotid Endarterectomy--an Evidence-Based Review: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2005;65:794-801.
5. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR et al. Analysis of Pooled Data from the Randomised Controlled Trials of Endarterectomy for Symptomatic Carotid Stenosis. Lancet 2003;361:107-116.
6. Neurologie NVv. Richtlijn Diagnostiek, Behandeling En Zorg Voor Patiënten Met Een Beroerte. 2008.
7. Spagnoli LG, Mauriello A, Sangiorgi G, Fratoni S, Bonanno E, Schwartz RS et al. Extracranial Thrombotically Active Carotid Plaque as a Risk Factor for Ischemic Stroke. JAMA : the journal of the American Medical Association 2004;292:1845-1852.
8. Redgrave JN, Lovett JK, Gallagher PJ, Rothwell PM. Histological Assessment of 526 Symptomatic Carotid Plaques in Relation to the Nature and Timing of Ischemic Symptoms: The Oxford Plaque Study. Circulation 2006;113:2320-2328.
9. Park AE, McCarthy WJ, Pearce WH, Matsumura JS, Yao JS. Carotid Plaque Morphology Correlates with Presenting Symptomatology. J Vasc Surg 1998;27:872-878; discussion 878-879.
10. Ballotta E, Da Giau G, Renon L. Carotid Plaque Gross Morphology and Clinical Presentation: A Prospective Study of 457 Carotid Artery Specimens. J Surg Res 2000;89:78-84.
11. Gao P, Chen ZQ, Bao YH, Jiao LQ, Ling F. Correlation between Carotid Intraplaque Hemorrhage and Clinical Symptoms: Systematic Review of Observational Studies. Stroke 2007;38:2382-2390.
12. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J et al. From Vulnerable Plaque to Vulnerable Patient: A Call for New Definitions and Risk Assessment Strategies: Part I. Circulation 2003;108:1664-1672.
13. Seeger JM, Barratt E, Lawson GA, Klingman N. The Relationship between Carotid Plaque Composition, Plaque Morphology, and Neurologic Symptoms. J Surg Res 1995;58:330-336.
14. Moreno PR, Purushothaman KR, Fuster V, Echeverri D, Truszczynska H, Sharma SK et al. Plaque Neovascularization Is Increased in Ruptured Atherosclerotic Lesions of Human Aorta: Implications for Plaque Vulnerability. Circulation 2004;110:2032-2038.
15. Sluimer JC, Kolodgie FD, Bijnens AP, Maxfield K, Pacheco E, Kutys B et al. Thin-Walled Microvessels in Human Coronary Atherosclerotic Plaques Show Incomplete Endothelial Junctions Relevance of Compromised Structural Integrity for Intraplaque Microvascular Leakage. J Am Coll Cardiol 2009;53:1517-1527.
16. Pei X, Wu B, Tang TY, Gillard JH, Li ZY. Fatigue Crack Growth under Pulsatile Pressure and Plaque Rupture. JACC Cardiovasc Imaging 2014;7:738-740.
17. Versluis A, Bank AJ, Douglas WH. Fatigue and Plaque Rupture in Myocardial Infarction. J Biomech 2006;39:339-347.
18. Calcagno C, Mani V, Ramachandran S, Fayad ZA. Dynamic Contrast Enhanced (Dce) Magnetic Resonance Imaging (Mri) of Atherosclerotic Plaque Angiogenesis. Angiogenesis 2010;13:87-99.
19. Gaens ME, Backes WH, Rozel S, Lipperts M, Sanders SN, Jaspers K et al. Dynamic Contrast-Enhanced Mr Imaging of Carotid Atherosclerotic Plaque: Model Selection, Reproducibility, and Validation. Radiology 2013;266:271-279.
20. Kerwin W. Quantitative Magnetic Resonance Imaging Analysis of Neovasculature Volume in Carotid Atherosclerotic Plaque. Circulation 2003;107:851-856.
21. Kerwin WS, O'Brien KD, Ferguson MS, Polissar N, Hatsukami TS, Yuan C. Inflammation in Carotid

Atherosclerotic Plaque: A Dynamic Contrast-Enhanced Mr Imaging Study1. Radiology 2006;241:459-468.
22. Kerwin WS, Oikawa M, Yuan C, Jarvik GP, Hatsukami TS. Mr Imaging of Adventitial Vasa Vasorum in Carotid Atherosclerosis. Magn Reson Med 2008;59:507-514.
23. Calcagno C, Cornily JC, Hyafil F, Rudd JHF, Briley-Saebo KC, Mani V et al. Detection of Neovessels in Atherosclerotic Plaques of Rabbits Using Dynamic Contrast Enhanced Mri and 18f-Fdg Pet. Arterioscler Thromb Vasc Biol 2008;28:1311-1317.
24. Calcagno C, Vucic E, Mani V, Goldschlager G, Fayad ZA. Reproducibility of Black Blood Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Aortic Plaques of Atherosclerotic Rabbits. J Magn Reson Imaging 2010;32:191-198.
25. Calcagno C, Ramachandran S, Izquierdo-Garcia D, Mani V, Millon A, Rosenbaum D et al. The Complementary Roles of Dynamic Contrast-Enhanced Mri and 18f-Fluorodeoxyglucose Pet/Ct for Imaging of Carotid Atherosclerosis. European journal of nuclear medicine and molecular imaging 2013;40:1884-1893.
26. Wang J, Liu H, Sun J, Xue H, Xie L, Yu S et al. Varying Correlation between 18f-Fluorodeoxyglucose Positron Emission Tomography and Dynamic Contrast-Enhanced Mri in Carotid Atherosclerosis: Implications for Plaque Inflammation. Stroke 2014;45:1842-1845.
27. Sun J, Song Y, Chen H, Kerwin WS, Hippe DS, Dong L et al. Adventitial Perfusion and Intraplaque Hemorrhage: A Dynamic Contrast-Enhanced Mri Study in the Carotid Artery. Stroke 2013;44:1031-1036.
28. Libby P. Inflammation in Atherosclerosis. Nature 2002;420:868-874.
29. Rudd JH, Warburton EA, Fryer TD, Jones HA, Clark JC, Antoun N et al. Imaging Atherosclerotic Plaque Inflammation with [18f]-Fluorodeoxyglucose Positron Emission Tomography. Circulation 2002;105:2708-2711.
30. Rudd JH, Myers KS, Bansilal S, Machac J, Rafique A, Farkouh M et al. (18)Fluorodeoxyglucose Positron Emission Tomography Imaging of Atherosclerotic Plaque Inflammation Is Highly Reproducible: Implications for Atherosclerosis Therapy Trials. J Am Coll Cardiol 2007;50:892-896.
31. Tawakol A, Migrino RQ, Hoffmann U, Abbara S, Houser S, Gewirtz H et al. Noninvasive in Vivo Measurement of Vascular Inflammation with F-18 Fluorodeoxyglucose Positron Emission Tomography. J Nucl Cardiol 2005;12:294-301.
32. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL et al. Resting Heart Rate in Cardiovascular Disease. J Am Coll Cardiol 2007;50:823-830.
33. Lévy S, Guize L. [Heart Rate, a Major Prognostic Factor of Cardiovascular Risk]. Therapie 2006;61:115-119.
34. Palatini P. Heart Rate as an Independent Risk Factor for Cardiovascular Disease: Current Evidence and Basic Mechanisms. Drugs 2007;67 Suppl 2:3-13.