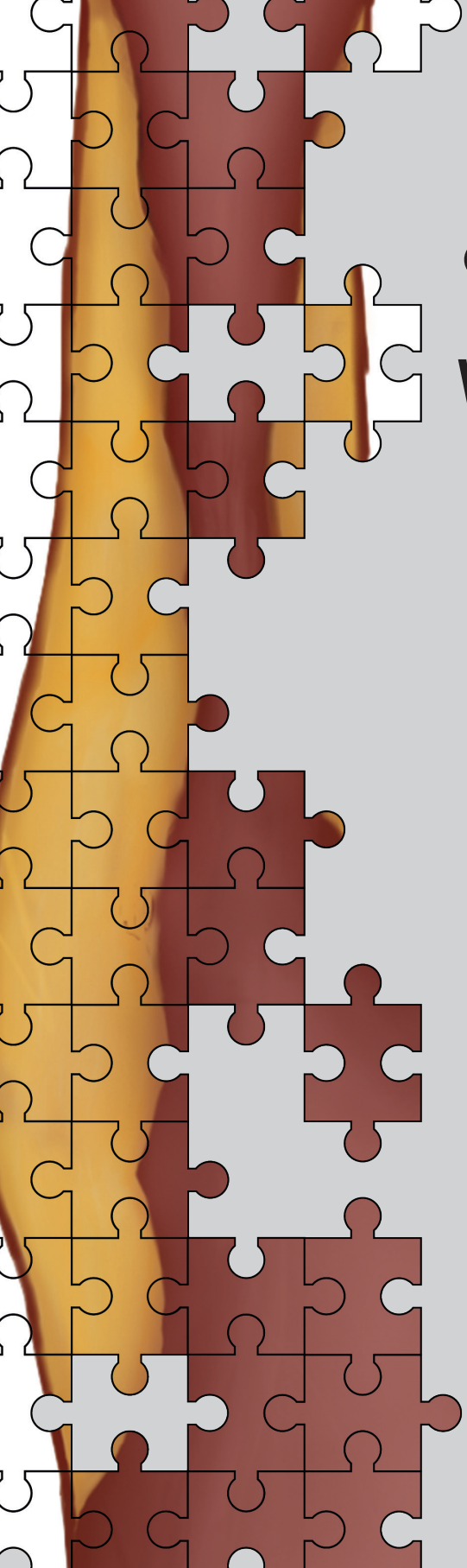
Dynamic contrast-enhanced MR imaging of artherosclerotic plaque microvasculature



Valorisation

Relevance

An estimated number of 240,000 people in the Netherlands are living with the consequences as a result of a stroke (1). In 2014, stroke accounted for 21% of all cardiovascular deaths, with a total number of nearly 10.000 deaths (2). Yearly, approximately 44,000 people are admitted to a hospital due to a stroke (1). Additionally, the medical costs involved in the diagnosis and treatment of stroke are substantial, accounting for 27.4% of the costs involved in cardiovascular care and 2.5% of the total medical costs in the Netherlands (3). It is expected that these numbers will increase over the coming decades, mainly because of the ageing population.

Hemorrhagic strokes account for approximately 10% of all strokes, while the remaining 90% are ischemic strokes (4). A considerable amount (15-20%) of ischemic strokes is caused by rupture of an atherosclerotic plaque in the (internal) carotid artery (5). Currently, risk stratification of patients with a stenosis of the carotid artery is based on the degree of luminal stenosis and symptomatology of the patient. Based on this, it is determined whether a carotid endarterectomy (CEA) is advised. Results from randomized trials have shown that CEA is beneficial for symptomatic patients with a carotid stenosis of 70-99% with a number needed to treat (NNT) of 6 to prevent one stroke in five years. However, for symptomatic patients with a stenosis of 50-69% CEA is only marginally effective with a NNT of 22 (6).

Histological studies on CEA specimens have shown that specific characteristics of atherosclerotic plaques have an increased incidence in symptomatic patients compared to asymptomatic patients (7-11). Features already identified as important hallmarks of plaque vulnerability are a lipid-rich necrotic core (LRNC) with a thin/ruptured fibrous cap (TRFC), presence of inflammatory cells, ulcerations, and intraplaque hemorrhage (IPH) (12). Additionally, it has been suggested that an increased microvasculature of the atherosclerotic plaque is an important marker of plaque vulnerability (13).

Identification of these “vulnerable plaques” with non-invasive imaging of the atherosclerotic vessel wall may provide opportunities for improved patient stratification. 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. Over the past years, technical improvements of non-invasive imaging methods have enabled in vivo visualization of these vulnerable plaque characteristics.. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) can be used to study and quantify the plaque microvasculature non-invasively (14).

The hypothesis of the present thesis was that non-invasive imaging of the plaque microvasculature with DCE-MRI may provide further insight in the atherosclerotic process. An increased insight in the role of the plaque microvasculature in the atherosclerotic process, may not only aid in identification of patients at increased risk, but may also provide novel targets for therapeutic interventions in the prevention and stabilization of atherosclerotic lesions.

Target groups

The results of this thesis are of interest for a broad range of professionals. First, it is of interest for scientists investigating the development of atherosclerotic plaques. Results from the present thesis and previous studies show that plaque microvasculature is an important determinant of atherosclerosis, since it is related to a number of processes related to plaque destabilization. Pharmacokinetic modelling of DCE-MRI data allows assessment of plaque microvasculature in a non-invasive manner. Therefore, the plaque microvasculature can be investigated in animal models and patients at multiple time points during the various stages of plaque development, even before the onset of clinical symptoms. This is of great advantage compared to histopathological studies, in which investigation of the plaque microvasculature can be performed only after euthanasia in animal studies and after CEA or at autopsy in patients. Non-invasive imaging of the microvasculature using DCE-MRI can contribute to the reduction of the amount of animals used in research.

Next to this, the results of this thesis are of interest for clinicians with a (research) interest in cerebrovascular disease. Currently, patients suffering from a recent ischemic cerebrovascular event undergo imaging of the carotid arteries for determination of the degree of carotid stenosis. Based on the results, patients may be referred to vascular surgery for CEA. However, there is increasing evidence, from the present thesis and other research, that patient stratification may be improved by assessment of the plaque components, including the plaque microvasculature. For further advancement of carotid plaque imaging, longitudinal studies are needed to investigate the predictive value of various plaque components, including plaque microvasculature for recurrent cerebrovascular events. For this purpose, the PARISk consortium in the Netherlands has performed longitudinal follow-up of patients that have suffered from a recent cerebrovascular event with patient follow-up of this trial finalized in December 2016, with results following in due time. The development of plaque microvasculature in relation to recurrent cerebrovascular events will be studied in a subgroup of these patients. After this prospective longitudinal study, it is important to investigate the potential value of dedicated imaging of carotid plaque microvasculature in a randomized surgery trial. Currently, imaging of various other carotid plaque components is already included in the recently started large randomized European Carotid Surgery Trial-2.

In addition to clinicians with a research interest in cerebrovascular diseases, the present thesis is also of general interest for clinicians. The results described in the present thesis may have impact on future guidelines for treatment of patients with carotid atherosclerotic plaque. Currently, patients with a mild to moderate stenosis are generally not referred to a vascular surgeon for surgical removal of the plaque, since randomized surgery trials performed in the early 90s of the last century have shown that CEA is only marginally effective for them. These patients in particular may benefit from improved personalized treatment.

The present thesis is also of interest for companies within the medical imaging industry. The results described in this thesis show the current state of DCE-MRI of the atherosclerotic plaque microvasculature. The development of advanced MR imaging protocols and analysis methods for quantification of the plaque microvasculature is expected to further advance

the clinical application of DCE-MR imaging. Additionally, companies developing (pharmacological) treatments or interventions targeted to the atherosclerotic plaque microvasculature may express interest in the results described in this thesis. DCE-MRI enables the investigation of the atherosclerotic plaque microvasculature non-invasively in animal models and patients. Compared to histopathological analysis, this enables evaluation of the treatment effect at multiple time points in the same subject, even before the onset of clinical symptoms. Thus, non-invasive imaging of the microvasculature using DCE-MRI can contribute to the reduction of the number of subjects, either animals or volunteers, that are required to study potential new treatments and their effect on the plaque microvasculature.

Activities / products

In the present thesis, analysis of the DCE-MRI data is performed using custom built software in Matlab (Natick, Mathworks, Massachusetts, United States). In addition, drawing of the lumen and vessel wall contours is performed manually by an experienced observer using the Vesselmass software package (Leiden University Medical Center, Leiden, The Netherlands). This process may be suitable in a research environment, in which analysis is performed by experienced observers. However, this may be challenging in multicenter studies with analysis being performed by an increased number of observers. Therefore, development of a software package in which the lumen and vessel wall contour drawing and data analysis can be performed (semi-)automatically is of great interest. This software package is likely to be of added value for the potential success of DCE-MRI in a research or future clinical setting with less experienced observers, which is needed for implementation of the technique in a wider setting. On this topic, substantial progress has already been made based upon data from the PARISK consortium (15) and a spin-off company from the University of Washington (16). However, main focus of previous studies was the identification of the various plaque components on MR images while work on semi-automatic analysis tools for DCE-MR data has been limited. Extension of this with methods to perform (non-rigid) transformations of DCE-MRI data might be an important step in the development of DCE-MRI software packages. These transformations may be useful to correct for (small) patient movements during the MR acquisition, enabling improved (local) quantification of the plaque microvasculature. Additionally, integration of the developed methods into current software packages of the major MR vendors will be an important improvement in the availability of these methods.

Innovation and Insights

Direct in vivo visualization of the plaque microvasculature is complicated due to the small size of the atherosclerotic plaque microvasculature (up to approximately 100 μm in diameter). However, pharmacokinetic modelling of DCE-MRI allows voxelwise estimation of microvascular properties. In the present thesis several innovations are presented and applied to increase insights in the role of the plaque microvasculature in atherosclerotic plaques.

Firstly, a novel, method for determination of the vascular input function (VIF) from phase MR images is described and applied for carotid DCE-MRI. The results from this thesis showed that VIFs derived from magnitude MR images were influenced by local blood flow velocity, leading to an underestimation of the contrast medium concentration in the vessel lumen. In turn, absolute values of determined pharmacokinetic parameters were influenced by the VIF, making direct cross-study comparisons of different studies difficult. Additionally, the results of the present thesis showed that the absolute values of the pharmacokinetic parameters determined may differ between different regions of the vascular wall. Therefore, the results of the present thesis clearly showed that the use of a standard imaging and data analysis protocol is essential, in particular for longitudinal studies of plaque microvasculature and for the future determination of risk thresholds.

One study described in the present thesis aimed to confirm the potential positive association between the plaque microvasculature and the presence of IPH, which has been suggested in previous research. However, the results of this chapter showed a decreased microvascular flow, density, or leakiness of the vessel wall in patients with IPH. Therefore, not only plaque microvasculature contributes to the development of IPH in carotid atherosclerosis. Based on our results, it is likely that additional factors, such as a disrupted plaque surface, also play an important role and should be investigated in future studies to fully understand the pathophysiology. Another important insight of the present thesis is that patients with a recent ischemic stroke showed an increased microvascular flow, density, or leakiness of the adventitia compared to patients with a recent transient ischemic attack (TIA) or ocular TIA (also known as amaurosis fugax). This association was independent of clinical risk factors. The potential association between plaque microvasculature and the type of recent cerebrovascular event has to be further confirmed in a prospective longitudinal study, however this finding may provide additional information on the value of DCE-MRI in the risk stratification of patients.

Finally, the present thesis demonstrated the ability of DCE-MRI as an evaluation tool for potential therapies in the treatment of atherosclerosis. The results showed that heart-rate reducing therapy was associated with a reduction in vulnerable plaque features. Therefore, the results of the present thesis added to current insights that plaque biomechanics and deformation may play an important role in the development of vulnerable plaque features. Therefore, heart rate reduction may be a potential target for plaque stabilization. To investigate the potential relationship between the plaque microvasculature and plaque biomechanics, including the underlying mechanisms, longitudinal studies incorporating both measurements should be performed in the future.

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