MRI based biomechanical parameters for carotid artery plaque vulnerability assessment

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Abstract

Carotid atherosclerotic plaques are a major cause of ischemic stroke. The biomechanical environment to which the arterial wall and plaque is subjected to plays an important role in the initiation, progression and rupture of carotid plaques. MRI is frequently used to characterize the morphology of a carotid plaque, but new developments in MRI enable more functional assessment of carotid plaques. In this review, MRI based biomechanical parameters are evaluated on their current status, clinical applicability, and future developments. Blood flow related biomechanical parameters, including endothelial wall shear stress and oscillatory shear index, have been shown to be related to plaque formation. Deriving these parameters directly from MRI flow measurements is feasible and has great potential for future carotid plaque development prediction. Blood pressure induced stresses in a plaque may exceed the tissue strength, potentially leading to plaque rupture. Multi-contrast MRI based stress calculations in combination with tissue strength assessment based on MRI inflammation imaging may provide a plaque stress-strength balance that can be used to assess the plaque rupture risk potential. Direct plaque strain analysis based on dynamic MRI is already able to identify local plaque displacement during the cardiac cycle. However, clinical evidence linking MRI strain to plaque vulnerability is still lacking. MRI based biomechanical parameters may lead to improved assessment of carotid plaque development and rupture risk. However, better MRI systems and faster sequences are required to improve the spatial and temporal resolution, as well as increase the image contrast and signal-to-noise ratio.

Introduction

Carotid atherosclerotic plaques are a major cause of ischemic stroke. Currently, the degree of carotid luminal stenosis is the only valid criterion that is associated with an increased risk of ischemic stroke and is used in clinical decision making to assess the severity of atherosclerotic disease. However, increasing evidence has shown a close association between the structure and morphology of the carotid plaque and patient clinical presentations (1) , plaque progression (2) and the probability of subsequent ischemic cerebrovascular events (3,4). Magnetic Resonance Imaging (MRI) is capable of characterizing carotid plaque morphology accurately (5) and with good reproducibility (6,7). Multicontrast MRI is generally used to identify the different plaque components. Using the basic contrast weightings T1, T2, and proton density, obtained with black blood sequences, the key features of a plaque can be identified, like fibrous tissue, lipid core (8), intraplaque hemorrhage (IPH) (9), and calcium (10). With high-resolution MRI, the status of the fibrous cap (FC) can even be assessed (11) and the intermediate and advanced lesions can be distinguished (12). New developments in MRI enable more functional assessment of carotid plaques, including detailed flow conditions (13,14), wall and plaque displacement and strain (15), and plaque inflammatory status (16).

The biomechanical environment, to which the arterial wall and plaque is subjected to, plays an important role in the initiation, development, and atherosclerotic plaque rupture. Blood flow related biomechanical parameters, including wall shear stress (WSS), have been shown to be involved in plaque initiation (17), plaque progression (18), and changes in plaque composition (19). Additionally, blood pressure induced stresses and strains in the plaque can exceed the material strength of the supporting tissues, potentially leading to plaque disruption and thrombosis (20).

In this review, the potential of MRI based biomechanical parameters to improve the accuracy in assessing carotid artery plaque vulnerability are discussed. The techniques detailed in this review focus on flow related biomechanical parameters, displacement and strain parameters, and on stress and failure strength of carotid plaque tissue. The current status of these techniques and the future developments will be explored, assessing whether they may translate into clinical practice.

Flow related biomechanical parameters

Plaque development has been shown to be related to low or low and oscillatory WSS, a force exerted on the endothelial cells by the flowing blood (17,21). WSS is also believed to play a role in plaque progression (18) and changes in plaque composition (19). Information on WSS and related biomechanical parameters can improve our understanding of carotid atherosclerosis (22,23).

WSS in a carotid artery bifurcation can be calculated using computational fluid dynamics (CFD) (24). Based on the lumen geometry, coupled with flow and pressure boundary conditions, the Navier-Stokes equations can be solved to obtain a high resolution blood velocity field throughout the complete geometry. WSS is calculated by multiplying the dynamic viscosity of blood with the shear rate, which is the radial spatial gradient of the velocity field at the vessel wall. However, CFD requires long computational times and accurate boundary conditions. Alternatively, WSS can be directly derived from the velocity field measured with phase contrast (PC) MRI (13,14,25–27). This way, the carotid artery shear rate can be obtained faster and without complex CFD calculations. These calculations were generally based on 2D PC MRI studies (28,29). Time averaged 3D flow data or time

resolved 3D PC MRI (also termed '4D flow MRI') data have recently been used to obtain 3D WSS distribution of carotid artery geometries (13,27).

To determine the local shear rate from an MRI velocity field, the vessel wall boundary needs to be identified, either by manual or automatic delineation of the MRI images (Figure 1) (30). The tangential and perpendicular velocity components close to the wall can be used in a curve fitting method to derive the shear rate at the wall using linear (31) or quadratic (32) fits or more advanced interpolation functions (27,33–36). To avoid incorrect shear rates due to over- or underestimated lumen areas, a minimum of 8 voxels in vessel diameter and a 10:1 signal-to-noise (SNR) ratio of the PC MRI is advised (27,37). Typically, 3D PC MRI carotid artery studies are performed with a spatial resolution in the order of 0.6-1 mm^3, but with a limited number of 8 to 10 time steps over the cardiac cycle. Although generally the patterns of MRI based WSS are similar to CFD based WSS (13), the levels of MRI based WSS are influenced by the spatial resolution of PC MRI (13,26,27,38,39). Especially for higher shear stress values, the accuracy of MRI based WSS tends to be significantly underestimated compared to CFD WSS (13,39). This underestimation increases with lower spatial resolution (13,26). Therefore, relative shear stress parameters are generally presented and may be more appropriate to evaluate as clinical markers, for instance by comparing patient specific shear stress maps with ensemble-average shear stress maps of a control populations (40).
When measuring blood flow velocities with PC MRI, a velocity encoding (VENC) value needs to be set, which determines the maximum range at which velocities can be measured. With a relative high VENC setting (higher than the maximum blood flow velocity), low velocity signals will be measured. With a relative low VENC setting, blood velocities exceeding the VENC will undergo phase wrapping and show up as an incorrect velocity. Such artifacts cannot be easily resolved with post processing and complicates the quantitative interpretation of the velocity maps. The VENC should therefore be appropriately chosen to comply with the maximum velocity in the area of interest. Other sources of inaccuracies in MRI velocity data include phase offset errors (41) and intravoxel dephasing (42). Although corrective methods are available for these errors, they may be dominant in specific geometries, e.g. highly stenotic or tortuous carotid arteries, making them unsuitable for current PC MRI sequences.
Besides WSS, studies have shown that changes in WSS direction over the cardiac cycle may promote atherosclerosis (43–45). These directional changes can be quantified by the oscillatory shear index (OSI) (46). OSI ranges between 0 and 0.5, where higher values indicate more variation in WSS direction. As OSI is a measure of temporal changes of the WSS, an accurate evaluation of MRI based OSI is only possible with time-dependent velocity information with high spatial and temporal resolutions. Although MRI based OSI is intrinsically challenging due to the trade-off between spatial resolution and temporal resolution, several studies demonstrated the feasibility of MRI based OSI in carotid arteries (29,39,47). Clinical evaluations are required to investigate the diagnostic value of MRI derived WSS and OSI.
Using CFD calculations, a variety of hemodynamic wall parameters have been evaluated and compared (23). The relative residence time (RRT) was shown to be a robust metric and might therefore be appropriate as a single metric to replace WSS and OSI to characterize low and oscillatory wall shear stress (23). More recently, new hemodynamic parameters have been suggested, such as localized normalized helicity of the flow (48) and transverse wall shear stress (transWSS), which characterizes the multi-directionality of the flow field (45). TransWSS seems to

localize better with plaque locations than time averaged WSS, OSI, or RRT, although clinical studies should be performed to evaluate whether it holds for MRI based hemodynamic measurements.

In the future, advanced MRI acceleration techniques can be used to reduce the imaging times and the noise levels, allowing MRI scans to be acquired at higher spatial and temporal resolutions (49–51). Deriving carotid shear stress directly from MR flow measurements seems to be feasible when all requirements are taken into account. However, clinical evidence that MRI based shear stress parameters relate to future clinical events still needs to be provided. As MRI based WSS analysis is more straightforward and less time consuming than CFD calculations, MRI based WSS has a great potential in improving the prognostication of future carotid plaque related clinical events.

Stress and strength parameters

The degree of carotid luminal stenosis as diagnostic criterion becomes less reliable in patients with mild to moderate carotid stenosis (52). Increasing evidence suggests that the physical characteristics of atherosclerotic plaques may have a greater potential to predict progression and clinical events than luminal stenosis alone (3,20).

A vulnerable carotid atherosclerotic plaque is characterized by a thin FC, a large, lipid-rich necrotic core, inflammatory cells, and frequently the presence of IPH. Symptomatic plaques are associated with FC rupture. IPH and FC rupture can be quantified accurately by *in vivo* high-resolution, multi-contrast MRI (53–55), and have shown to predict future clinical events in symptomatic (56) and asymptomatic (4,57) patients. FC rupture is thought to be the precipitating factor in the majority of clinical events, and occurs when the mechanical loading due to flow and pressure exceeds the strength of the tissue. Indeed, high mechanical stress concentrations in plaques were associated with fissuring in both coronary (58) and carotid (20) plaques. Furthermore, stress levels within a FC can differentiate symptomatic from asymptomatic patients (59), and are associated with subsequent cerebrovascular ischemic events in symptomatic patients (60).

The combination of MR-depicted compositional plaque features and mechanical analysis may have the potential for a more accurate plaque vulnerability assessment. Structural stress levels within the plaque cannot be directly measured. Finite element method (FEM)-based analysis has been widely used to estimate stresses in atherosclerotic plaques indirectly (20,61,62). For these stress calculations, the plaque geometry, tissue material properties, and loading conditions are required (63). The loading conditions are generally estimated using brachial artery pressures.

Successful FEM plaque analysis requires intensive manual image processing, geometrical reconstruction of the plaque and considerable computational time. In particular, each model may take a few days to successfully perform a 3D fluid structure interaction (FSI) analysis, which is thought to be the most accurate computational strategy (64). A fast computational protocol is, therefore, needed if this technique is to be fully translated into the clinic. For mild to moderately stenotic carotid plaques, a 3D structure-only model is reasonably accurate and computationally inexpensive, as compared with 3D FSI simulations (64). Although in 2D simulations the qualitative stress distribution in the plaque is mainly unaltered, 3D simulations seem to be a requirement for accurate peak stress calculations (65).

Carotid plaque geometry (lumen, lipid core, outer wall, calcifications, and IPH) can be reconstructed from multi-contrast MRI, using manual or automatic segmentation techniques (Figure 2). The accuracy of the segmentation is frequently limited by the imaging resolution. Most clinically oriented FEM analyses are based on 2D fast spin echo (FSE) MRI with an in-plane resolution around 0.4x0.4 mm^2 and a slice thickness of 2-3 mm (20,66). Due to these thick slices, partial volume effects may

occur, leading to a misrepresentation of plaque characteristics. Additionally, Imaging the plaque under an oblique plane orientation can obscure a FC thickness assessment, especially when the slice thickness is much larger than the in-plane image resolution (67). Advanced 3D isotropic MR sequences generally exhibit a lower in-plane resolution (0.6-1 mm), but can image a larger volume with thinner slices (68–70). A thin FC, a key feature of a high-risk plaque (71), may be hardly visible. Thus, geometrical assessment of carotid plaques based on MRI is currently only reliable for plaques with thicker caps. Calcification, IPH and lipid-rich necrotic cores can be identified with high resolution, multi-contrast MRI with a moderate-to-good sensitivity and specificity (5).

Given de limited dimensions of the vessel wall and plaques components, high resolution imaging is desirable. However, pushing the spatial resolution to the extreme is impossible because of scan time limitations and the available SNR. Over de past decade the use of a dedicated phased array neck surface coil with either 4 or 8 channels has become more and more standard for carotid imaging [Balu et al. J Magn Res Imag 2009]. The use of either a conventional head and neck coil or a single element surface coil does not deliver sufficient image quality.

Recent advances in quantitative MR sequences, such as T_1 and T_2 mapping (72) have the potential to further improve the discriminatory power between different tissue types. Further improvements in resolution, SNR, and clinically feasible imaging times (about 10-15 minutes) may be achieved with higher magnetic field strength, such as 7 Tesla MRI (73). Additionally, novel MRI sequences (74,75) and acceleration techniques (76) are needed to reduce imaging time and to improve image resolution and SNR.

A further important aspect to plaque stress calculations regards the material properties of the atherosclerotic plaque tissues. Experimental measurements of the material properties are limited (77–80), in particular those that consider nonlinear material behavior. Furthermore, the experimental measurements generally show a large variation in material properties within and between patients. This variation may have a great impact in stress calculations, in particular when the FC is thin (81,82). Displacement or strain data of carotid plaques measured with dynamic MRI acquisitions can also be used to evaluate the mechanical properties of the tissue locally (83–85). In the next section, MRI techniques are discussed that may be used to measure deformation on strain in a carotid plaque in vivo. To derive plaque material properties, biomechanical FEM models are created from multi-contrast MRI that reflect the geometry of the plaque. Displacements calculated with FEM can then be matched with the MRI measured displacements by optimizing the material properties of the plaque components in the model (83). Based on the patient-specific estimate of the material plaque properties, FEM can provide stresses and strains in a plaque. As the accuracy with which the material properties can be estimated depends on the accuracy of the plaque geometry and the accuracy of the displacement calculations with MRI, validation is needed to truly assess the reliability of these techniques. So far, only fully elastic material models are used to assess the mechanical behavior of arteries based on MRI. The intrinsic viscous properties of arterial tissue may play a role in the general behavior of the tissue and the stress/strain response due to the cyclic blood pressure. To estimate the viscous effects, also pressure waveforms are required that are time-registered with the area variation measurements of the vessel. Pressure waveforms in the carotid artery can be measured using applanation tonometry, although MRI based methods have also been proposed, based on Fourier velocity encoded M-mode MRI (86).

When stresses within a plaque are computed, a strength threshold is needed as a reference, above which the lesion may be unstable and induce subsequent ischemic events. The 300 kPa threshold possible is the most widely used (63). However, this threshold is based on mechanical testing of

human aortic plaque caps (87) and different vascular territories likely contain plaques with different morphological and mechanical features. In order to establish a useful strength threshold for FC, direct material testing is necessary, for instance following the suggested testing protocol from Walsh et al. (2014) (88). The study that provided the 300 kPa threshold also showed that FCs of ruptured plaques exhibit a higher degree of inflammation than caps from unruptured plaques (87). Increased inflammatory status of a plaque can lead to degradation of the extracellular matrix and thereby weakening of the plaque. Information on the inflammatory status may therefore provide vital information on the (relative) strength of a plaque. Molecular imaging may provide in vivo information on the plaque inflammatory status. Currently, vascular inflammation is best measured by co-registration of 18-F-FDG PET and CT imaging [Alie et al. Clin Med Insights Cardiol. 2015]. More recently, PET/MRI was proposed for the excellent soft tissue contrast of MRI, but this technique is not frequently used in the clinic yet. Research in the MRI field has focused on specific MRI acquisition sequences and targeted MRI contrast media to evaluate the plaque inflammatory status with MRI alone. These initiatives are currently being developed and validated against PET/CT imaging and it may take a number of years before they can be employed in the clinic (16,89,90).

Displacement and strain parameters

The composition of an atherosclerotic plaque generally has an effect on the deformation of the plaque over the cardiac cycle; soft plaques will deform more than stiff plaques under the same pressure conditions. Determining plaque deformation may therefore be valuable for an improved assessment of plaque composition. Previous studies in coronary and femoral artery plaques showed that, with invasive ultrasound measurements, strain values can indeed serve as a surrogate marker for plaque composition and vulnerability (91,92).
Different MRI techniques may be used to derive carotid artery deformation in vivo (15). Cine MRI is capable of recording carotid movement over the cardiac cycle. It is a widely used imaging protocol with acceptable spatial (0.6-1 mm^3) and temporal resolutions (20-50 ms) and the starting point of many post-processing techniques to derive plaque deformation (83,93). A drawback of conventional cine MRI is that only the lumen boundary is visible, whereas the vessel wall is hardly visible due to the limited spatial resolution and SNR of the wall compared to the lumen. By applying blood suppression (Black Blood imaging), the interface between the lumen and wall becomes clearer, however, the temporal resolution decreases due to the extra inversion pulses required for blood suppression. Alternatively, separate scans can be acquired for each heart phase, which results in even longer scan times. Although PC MRI is mainly used to measure blood flow velocity, it may also be used to measure the velocity of the vessel wall. Because of the low vessel wall velocity, a relatively low VENC should be used, in the order of 1-5 cm/s. This, together with the need for an extra reference image, lowers the temporal resolution even more, compared to cine MRI. Instead of measuring velocity, a modified PC MRI protocol called Displacement Encoding using Stimulated Echoes (DENSE) can be used to record tissue displacement (94). Strain encoding (SENC) MRI techniques are able to directly encode tissue strain in the acquired images, but can only be used for through-plane strain data (95), and not in-plane radial strain imaging. Also, high temporal resolution requirements lead to spatial resolutions unfit for carotid artery imaging (96). Future developments in DENSE or PC MRI sequences may provide accurate displacement or velocity data of the arterial wall. For now, the most promising techniques to derive carotid artery plaque deformation are post-processing techniques based on black blood cine MRI data (figure 3). The effectiveness of these

techniques highly depends on the spatial and temporal resolutions and on the contrast within the MR images. In general, a voxel size of 0.6 mm^3 or lower seems to provide enough voxels for image registration. However, increasing the spatial resolution automatically means a decrease in temporal resolution, because of a longer required read-out time per voxel. Additionally, smaller voxels produce less signal, thereby lowering the SNR. The optimal set of spatiotemporal resolutions and SNR is therefore dependent on the measure (displacement, velocity, or strain), the MRI hardware at hand, and the desired application. Post-processing techniques like non-rigid image registration techniques strongly rely on the quality of the images and are also susceptible for errors due to out-of-plane motion or inadequate registration parameters [Nederveen et al. J Biomech 2014].

MR strain imaging is a potential non-invasive imaging tool to assess carotid artery plaque vulnerability. By identifying high strain spots, that correspond to soft plaque regions, vulnerable plaques may be distinguished from stable plaques and clinical decision making may benefit from this. To identify soft spots (high strain) in carotid artery plaques, the best variable is tissue strain, as assessed using intravascular palpography (91). As strain is a derivative of displacement it is, however, highly susceptible to noise. Evaluating displacement itself may be more promising, as it is less noisy and more homogeneous over the plaque. The disadvantage of displacement measurements is that local tissue inhomogeneities may be impossible to identify. As stresses and strains in circumferential direction of a plaque are the most relevant parameters for plaque rupture, the circumferential displacement seems to be the most appropriate parameter for plaque type evaluation. Besides serving as a potential risk parameter, cyclic displacement of the carotid artery and plaque may also be used as input for fluid-structure interaction (FSI) models. In these models, carotid flow analyses are done while accounting for the cyclic movement of the solid tissue [Yang et al. J. Biomech. 2010; Huang et al. J Biomech 2014]. By measuring the movement, modeling assumptions like wall thickness and stiffness can be avoided, increasing the accuracy of the FSI models.

Identifying stable plaques with significant luminal narrowing using MR strain imaging may lead to re-evaluation of the indications for carotid endarterectomy. On the other hand, identifying vulnerable plaques with MR strain imaging which do not cause substantial lumen narrowing may improve clinical decision making. Although in research settings substantial advances have been made and plausible deformation and strain data of carotid arteries have been shown, current clinical MR machines are generally unable to run the required experimental MRI protocols and to provide the spatial and temporal resolutions required to measure carotid plaque deformations.

Conclusions

Carotid atherosclerotic plaques can be non-invasively characterized by high resolution multi-contrast MRI protocols. Plaque geometry and typical plaque features can be derived by combining multiple MRI sequences. However, new MRI-based techniques have been developed focusing on the functional behavior of tissue. In this review, we presented the current status of MRI-based biomechanical analyses that have the potential to improve carotid artery plaque diagnostics. At this moment, limited spatial and temporal resolutions and low SNR limit the accuracy of these biomechanical analyses. In the future, better MRI systems, faster sequences, and more dedicated MR imaging protocols will become available, specifically for carotid artery plaques. Validation of the discussed techniques are essential and will become within reach with improved MR techniques.

Although significant advances still need to be made, MR flow imaging, MRI-based biomechanical modeling, and MR strain imaging may, together or separately, lead to improved risk assessment of carotid artery plaques and may provide input for the clinical decision making of carotid endarterectomy or medical treatment.

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