

Atherosclerotic plaque fibrous cap assessment under an oblique scan plane orientation in carotid MRI

Harm A. Nieuwstadt¹, Aad van der Lugt², Zaid A.M. Kassab^{1,2}, Marcel Breeuwer^{3,4}, Anton F.W. van der Steen^{1,5}, Frank J.H. Gijsen¹

¹Department of Biomedical Engineering, ²Department of Radiology, Erasmus MC, Rotterdam, the Netherlands; ³Department of MR Clinical Science, Philips Healthcare, Best, the Netherlands; ⁴Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, the Netherlands; ⁵Department of Imaging Science and Technology, Delft University of Technology, Delft, the Netherlands

Correspondence to: Frank Gijsen. Department of Biomedical Engineering, Erasmus Medical Center, Rotterdam, Biomechanics Laboratory Ee2338, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands. Email: f.gijsen@erasmusmc.nl.

Abstract: Carotid magnetic resonance imaging (MRI) is used to noninvasively assess atherosclerotic plaque fibrous cap (FC) status, which is closely related to ischemic stroke. Acquiring anisotropic voxels improves in-plane visualization, however, an oblique scan plane orientation could then obscure a FC (i.e., contrast below the noise level) and thus impair a reliable status assessment. To quantify this, we performed single-slice numerical simulations of a clinical 3.0T, 2D T1-weighted, black-blood, contrast-enhanced pulse sequence with various voxel dimensions: in-plane voxel size of 0.62 mm × 0.62 mm and 0.31 mm × 0.31 mm, slice thickness of 1, 2, and 3 mm. Idealized plaque models (FC thickness of 0.5, 1, and 1.5 mm) were imaged at various scan plane angles (0°–40° in steps of 10°), and the FC contrast was quantified. We found that when imaging thin FCs with anisotropic voxels, the FC contrast decreased when the scan plane orientation angle increased. However, a reduced in-plane voxel size at the cost of an increased slice thickness often led to enhanced FC contrast even in the presence of scan plane orientation angles of up to 40°. It can be concluded that while isotropic-voxel imaging eliminates the issue of scan plane obliqueness, it comes at the cost of reduced FC contrast, thus likely decreasing the reliability of FC status assessment in carotid MRI. If scan plane orientation obliquity at the slice of interest is moderate (<40°) or otherwise diminished through careful scan planning, voxel anisotropy could increase FC contrast and, in effect, increase the reliability of FC status assessment.

Keywords: Magnetic resonance imaging (MRI); stroke; atherosclerosis; simulations; fibrous cap (FC)

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Introduction

Carotid magnetic resonance imaging (MRI) is used to noninvasively image atherosclerotic plaques at the carotid bifurcation (1,2). Of particular relevance are rupture-prone, vulnerable plaques, which are morphologically constituted of a large lipid-rich necrotic core (LRNC) covered by a thin fibrous cap (FC) (3,4). Carotid plaque rupture is a major cause of transient ischemic attacks and ischemic strokes. The principal advantage of carotid MRI is its high soft-

tissue contrast, which allows visualization of individual plaque components (5,6). Black-blood, contrast-enhanced MRI sequences assist in FC visualization by enhancing the FC signal relative to the adjacent LRNC (7-9). However, quantitative thickness measurements of FCs are prone to error due to the limited in-plane voxel size with respect to FC thickness (10-12). Instead, a more straightforward and more reliable qualitative assessment of FC status (e.g., thick, thin, and ruptured) *in vivo* through carotid MRI has been proven to be clinically highly relevant (13-19).

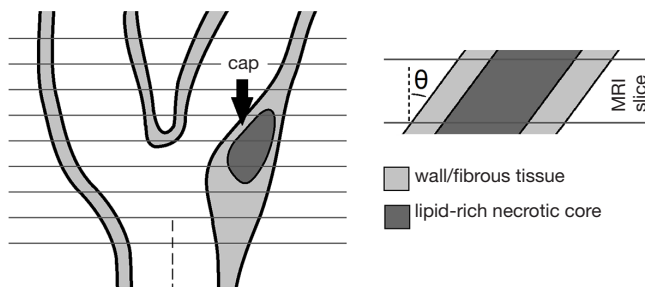


Figure 1 Illustration of a longitudinal cross-section of a carotid bifurcation and MRI slice positioning. Slices from 2D carotid magnetic resonance imaging (MRI) protocols are aligned along the common carotid artery axis, which can cause an oblique scan plane orientation (imaging at an angle θ) at the slice covering the fibrous cap (FC), obscuring the FC and impairing a reliable status assessment.

Most clinical protocols today employ 2D multi-slice sequences and acquire anisotropic voxels (20). With anisotropic voxels, one can reach a smaller in-plane voxel size while maintaining the same voxel volume and signal-to-noise ratio (SNR) because of a relatively larger slice thickness (21). Recent advances in 3D carotid MRI pulse sequence design enable isotropic-voxel plaque imaging (22). Irrespective of the acquisition methodology (i.e., 2D or 3D), the choice of a relatively smaller in-plane voxel size will facilitate visualization of in-plane plaque features—such as thin FCs—by reducing in-plane partial volume effects and point-spread function (PSF) signal spreading (10,11). On the downside, axial partial volume effects in anisotropic voxels can not only be caused by plaque morphological variations in the slice-select direction within a slice (23,24), but also by an oblique scan plane orientation in relation to the localized FC orientation (25). In clinical practice, the slice-select direction is typically aligned with the common carotid axis proximal to the bifurcation, using a localizer on an MR angiography scout scan in a sagittal view (Figure 1). A plaque could therefore be imaged at an angle, which, on top of the already limited in-plane resolution, might decrease FC contrast, thus preventing a reliable status assessment. A FC is often the smallest feature of a plaque, making it the most susceptible to obliquity artifacts. In addition, a plaque is usually present at locations with large geometrical variations or vessel angulations (26,27). An oblique scan plane orientation affects carotid wall area measurements and could influence FC imaging (28). Whether or not imaging at a certain angle would obscure a

FC and prevent its differentiation from the adjacent LRNC depends on numerous factors, such as the scan protocol, tissue relaxation times, FC thickness, in-plane resolution, slice thickness, and SNR. In this study, we took into account all of these factors for a typical 2D contrast-enhanced T_1 -weighted pulse sequence and quantified the influence of scan plane obliquity and voxel dimensions on FC contrast.

Methods

We performed numerical MRI simulations of a typical 2D carotid MRI protocol on idealized plaque models and varied the cap thickness (d), the acquired in-plane voxel size, the slice thickness (δ), and the scan plane orientation angle (θ). The advantage of MRI simulations is that they allow a perfectly controlled environment where single parameters can be varied, which is impracticable in a patient study. For a reliable FC status assessment, the FC contrast should be sufficiently high in relation to the adjacent LRNC contrast and the SNR. We therefore quantified the effects of the aforementioned parameters on FC contrast. Because we focused on scan plane obliquity, axial plaque morphological variations were not taken into account. Scan plane obliquity was confined to the direction of relevance: the short axis of the FC (i.e., the FC thickness direction). Each methodological step will now be discussed in more detail.

Trigonometric model

Before commencing the MRI simulations, it was important to gain a feeling for the combined effects of θ , δ , and d on the spatial distribution of FC tissue within a slice in the direction of angulation (x). We therefore created a simple analytical 1D trigonometric model (Figure 2A). To maintain generality at this point, we confined ourselves to a geometrical analysis and focused on $\lambda(x)$: the fraction [%] of tissue at location x occupied by the FC. Location B is given by $\delta \tan(\theta)$, and location C by $d/\cos(\theta)$. Also note that apparent FC thickness increased with a factor $1/\cos(\theta)$. These simple geometrical relationships helped explain some observations from the MRI simulations.

Idealized plaque models

Three idealized carotid plaque models with a single LRNC and no other components were created, each with only a different FC thickness: 0.5, 1, and 1.5 mm. Although FCs of vulnerable carotid plaques can be thinner than

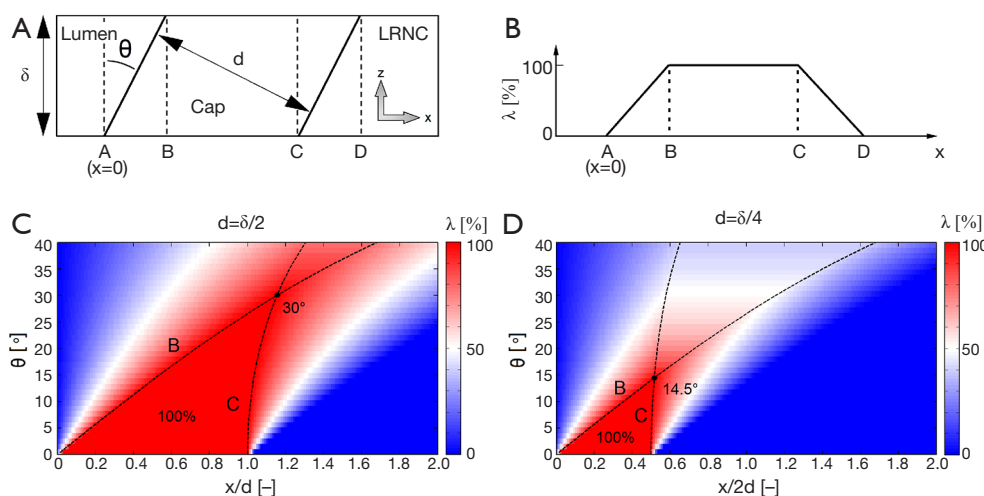


Figure 2 (A) A 1-dimensional trigonometric model illustrates the effects of the scan plane angle (θ), slice thickness δ , and cap thickness d on $\lambda(x)$: the fraction of tissue occupied by the FC within a slice; (B) Sketch of $\lambda(x)$ for a certain θ ; (C) $\lambda(x, \theta)$ for $d = \delta/2$; (D) $\lambda(x, \theta)$ for $d = \delta/4$.

0.5 mm (10,29), we did not include these, because they would fall below the typical in-plane acquired voxel size of current clinical carotid MRI protocols, and would become obscured regardless of scan plane obliquity (16). The lumen diameter (4.5 mm), outer wall diameter (9.0 mm), LRNC shape, LRNC size (14 mm²), and LRNC width (2.4 mm) of the idealized models were kept unaltered and were based on typical dimensions of diseased carotid arteries. The modeled plaque tissues were fibrous tissue, LRNC, and the sternocleidomastoid muscle (used as background), and were assigned T_1 relaxation times of 680, 1,220, and 1,412 ms respectively, and a fixed T_2 of 50 ms for the MRI simulations (11). The models were angulated from 0° to 40° in steps of 10° with respect to the axial axis. The direction of the FC thickness was aligned with the phase direction in the MRI simulations and likewise was the direction of scan plane obliquity. This choice was made because Gibbs ringing artifacts manifesting predominantly in the frequency (measurement) direction could influence tissue intensity at the edge of the lumen (11,28).

MRI simulations

A standard clinically applied 3.0T, 2D T1-weighted turbo spin-echo, contrast-enhanced, black-blood pulse sequence used for FC imaging was implemented in the Juelich Extensible MRI Simulator (JEMRIS) (30). A detailed description of this particular implementation including an evaluation with patient images can be found in (11). The simulated pulse sequence used non-selective radio

frequency pulses, which eliminated the need for slice selection and spoiler gradients, resulting in single slice simulations. The repetition and echo timings were 800 and 10 ms, respectively. The simulated sequence covered a field-of-view of 37 mm × 37 mm with a matrix size of 60 × 60 which yielded the same in-plane acquisition voxel size as the original clinical protocol: 0.62 mm × 0.62 mm. The reduced field-of-view was obtained by decreasing the number of shots while keeping both the turbo-spin echo factor (equal to 10) and k-space filling order (centric) unaltered. A reconstructed voxel size of 0.31 mm × 0.31 mm was achieved after zero-padding of the k-space prior to Fourier transforming. The slice thickness of the original clinical protocol was $\delta = 2$ mm. For this study, we additionally simulated slice thicknesses of 1 and 3 mm. A modified protocol with a smaller in-plane acquired voxel size of 0.31 mm × 0.31 mm (0.16 mm × 0.16 mm reconstructed) was also simulated. Such changes in voxel sizes would affect the SNR and/or scan time in clinical systems according to the SNR equation. Because our simulations yielded noise-free images, our FC contrast findings can be assessed post-hoc for any arbitrary SNR levels. The actual measure for resolving small features in MRI is the PSF, and its importance is the reason we performed MRI simulations instead of simply geometrical re-sampling (11). The full-width at half-maximum of the PSF in the phase direction (which was the direction of angulation) in the image space was 1.1 mm for the original 0.62 mm × 0.62 mm protocol and 0.55 mm for the modified 0.31 mm × 0.31 mm protocol. The simulations were performed with a high spin-

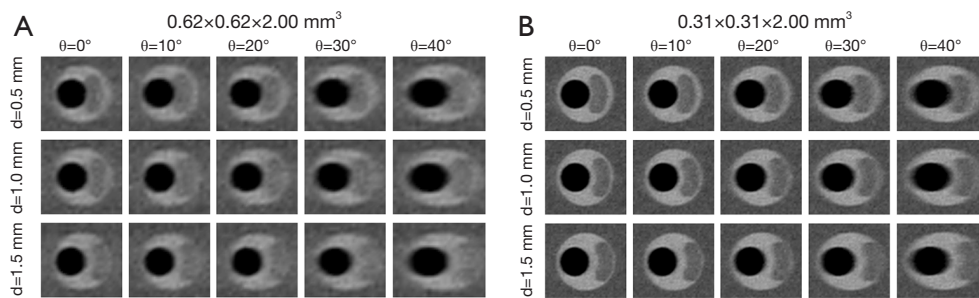


Figure 3 Simulated MR images for the case of $\delta=2$ mm. Each plaque model with different FC thicknesses ($d=0.5$, 1, and 1.5 mm) is imaged at five angles (0° to 40°). (A) Voxel size of $0.62 \text{ mm} \times 0.62 \text{ mm} \times 2.00 \text{ mm}$; (B) Voxel size of $0.31 \text{ mm} \times 0.31 \text{ mm} \times 2.00 \text{ mm}$. Rician distributed noise was added to these example images to yield a typical SNR of 16.7 (11).

discretization, with an average of $\sim 8,000$ simulated spins per voxel. Black-blood imaging was simulated by defining no magnetization of the luminal area. Motion artifacts were not simulated.

Analysis

For each resulting noise-free ($1/\text{SNR}=0$) simulated carotid MR image, the FC contrast was computed. The FC contrast was defined as the maximum FC intensity relative to the minimum intensity of the adjacent LRNC, and therefore computed with the following contrast-to-tissue equation: $(I_{\text{cap,max}} - I_{\text{LRNC,min}})/I_{\text{LRNC,min}}$ (31). Note that the theoretical upper-limit of the FC contrast, $C_{\text{FC,max}}$, can be derived from the repetition time (TR) and the apparent T_1 relaxation times (tissues had identical T_2 times) of LRNC and fibrous tissues:

$$C_{\text{FC,max}} = \frac{e^{\left(\frac{-TR}{T_{1\text{LRNC}}}\right)} - e^{\left(\frac{-TR}{T_{1\text{fibrous}}}\right)}}{1 - e^{\left(\frac{-TR}{T_{1\text{LRNC}}}\right)}}$$

With the modeled tissue T_1 relaxation times, the theoretically maximum FC contrast with no partial volume effects or PSF signal spreading was equal to 0.44. The SNR was defined as the reciprocal of the coefficient of variation. This definition enabled a direct comparison between FC contrast and $1/\text{SNR}$, because if the FC contrast would be lower than $1/\text{SNR}$ (i.e., the relative noise level), the FC would likely be obscured. We also asked one (blinded) MRI reader (Z.K.) to measure the FC thickness on a set of images with $\delta=2$ mm and with added noise ($\text{SNR}=16.7$), in the situation where the FC was not judged as obscured by that reader. The images were presented in randomized order on five separate occasions.

Results

Trigonometric model

We first studied our 1D geometrical model. In *Figure 2*, we graph two cases: $d=\delta/2$ (*Figure 2C*) and $d=\delta/4$ (*Figure 2D*) for $\theta=0^\circ$ to 40° . We defined a critical angle, $\theta_c = \sin^{-1}(d/\delta)$, when $B=C$ (*Figure 2B*). This critical angle represents the smallest angle at which less than 100% at any location x is occupied by FC tissue. For $d=\delta/2$, $\theta_c=30^\circ$, and for $d=\delta/4$, $\theta_c=14.5^\circ$. So, interestingly, in the limit of a hypothetical in-plane voxel size $\ll d$, no obscurement of the FC should occur for $\theta < 30^\circ$ in the case of $d=\delta/2$. However, for $d=\delta/4$, the critical angle dropped to only 14.5° . Because this is just a geometrical analysis, the critical angle—a simple indicative but rather strict measure—does not directly translate to MR imaging, where the in-plane voxel size (typically $\sim d$), PSF, and SNR play significant roles as well.

MRI simulations

Simulated MR images for the case of $\delta=2$ mm are shown in *Figure 3*. The scan plane obliquity angle θ was found to have a strong effect on the appearance of FCs in certain configurations of the parameters studied. A cap of 0.5 mm thickness was already indistinguishable at $\theta=0^\circ$ for an in-plane acquired voxel size of $0.62 \text{ mm} \times 0.62 \text{ mm}$, while a cap of 1.0 mm (hardly visible at $\theta=0^\circ$) became obscured at 40° . For an acquired in-plane voxel size of $0.31 \text{ mm} \times 0.31 \text{ mm}$, a cap of 0.5 mm, clearly visible at $\theta=0^\circ$, was obscured at $\theta=40^\circ$. A FC of 1.5 mm thickness remained visible up to $\theta=40^\circ$. In general, thicker FCs appeared to be largely insensitive to scan plane obliquity, especially when imaged at the higher in-plane resolution. Increasing θ led to a reduction in FC contrast. FC contrast was clearly higher for

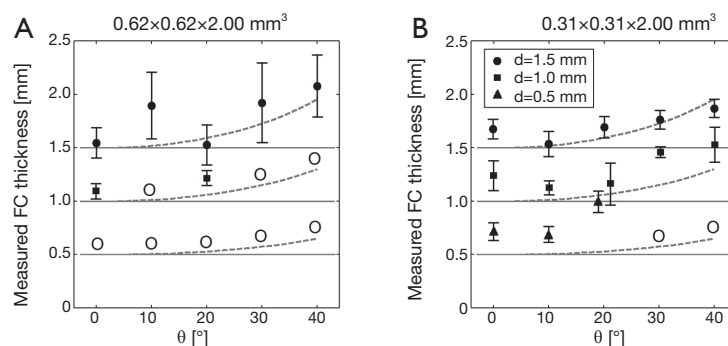


Figure 4 Manual FC thickness measurements ($n=5$, mean $\pm$ standard deviation indicated) on images in *Figure 3* ($\text{SNR}=16.7$, $\delta=2$ mm). The dotted grey curves represent $d/\cos(\theta)$: the apparent FC thickness. FCs judged as obscured by the MRI reader are indicated with an O ('obscured') and no thickness measurements were performed. (A) Data for a voxel size of $0.62 \text{ mm} \times 0.62 \text{ mm} \times 2.00 \text{ mm}$; (B) data for a voxel size of $0.31 \text{ mm} \times 0.31 \text{ mm} \times 2.00 \text{ mm}$. Legend in (B) also applies to (A). FC, fibrous cap.

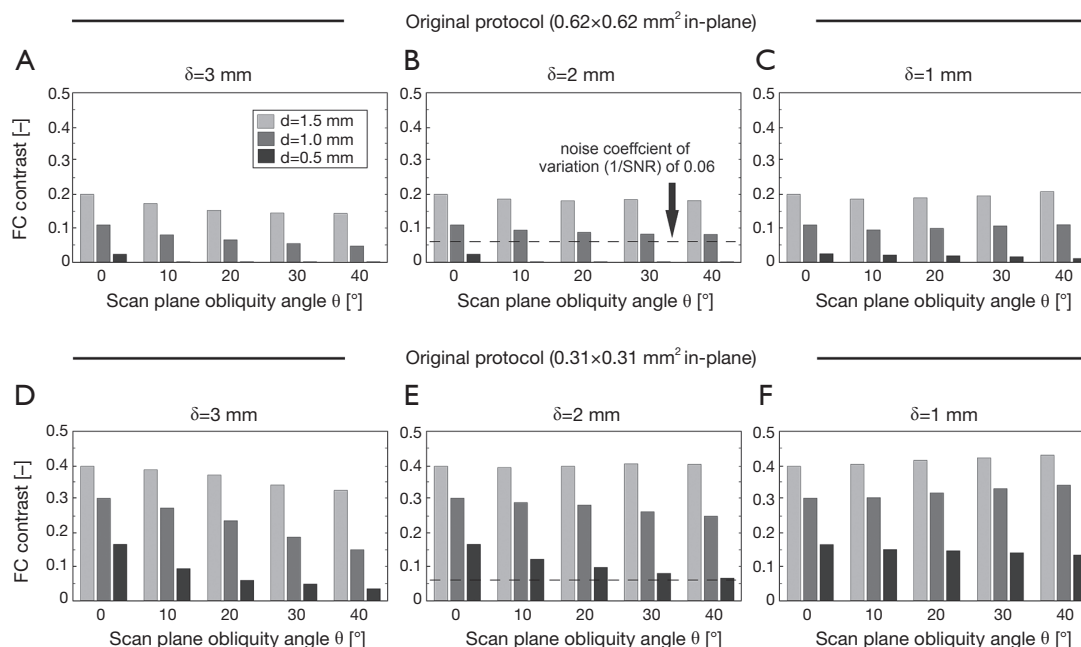


Figure 5 FC contrast is shown as a function of the scan plane angle (θ). Each graph (A-F) contains data for a specific slice thickness (δ) and in-plane acquired voxel size. Legend in (A) applies to all six graphs. The dotted horizontal line in (B, E) represents the $1/\text{SNR}$ line for the example $\text{SNR}=16.7$. FC, fibrous cap.

thicker caps and for the $0.31 \text{ mm} \times 0.31 \text{ mm}$ protocol, due to reduced in-plane partial volume effects.

The results of the manual FC thickness measurements (for the case with $\delta=2$ mm and $\text{SNR}=16.7$) are shown in *Figure 4*. In general, the overestimation of FC thickness increased for increasing θ . For example, the thickness of a 1.5 mm FC was measured as 1.55 ± 0.14 mm for $\theta=0^\circ$, and as 2.08 ± 0.29 mm for $\theta=40^\circ$ with the original $0.62 \text{ mm} \times 0.62 \text{ mm}$ protocol. For the modified $0.31 \text{ mm} \times 0.31 \text{ mm}$ protocol, the thickness of a

FC of 1.5 mm was measured as 1.67 ± 0.09 mm for $\theta=0^\circ$, and as 1.87 ± 0.08 mm for $\theta=40^\circ$.

The FC contrast as a function of θ for all plaque models and scan parameters with $1/\text{SNR}=0$ is shown in *Figure 5*. FC contrast became less dependent on θ for larger d , smaller δ , or a larger in-plane voxel size (thus approaching isotropic voxels). In fact, FC contrast even slightly increased for increasing θ in the $\delta=1$ mm case. In general, a thicker FC, or the use of a high in-plane resolution (anisotropic)

protocol, led to significantly increased FC contrast. These two factors, in many cases, outweighed the influence of scan plane obliquity on FC contrast. *Figure 5* provides quantitative data on how the FC contrast depends on the studied scan parameters. With the SNR and imaging parameters known, it is now possible to determine which FCs would become indistinguishable. For example, consider the case where $\text{SNR}=16.7$ and $\delta=2$ mm. When imaged with an acquired voxel size of $0.62 \text{ mm} \times 0.62 \text{ mm} \times 2.00 \text{ mm}$ at $\theta=40^\circ$, the contrasts of FCs of 0.5 and 1.0 mm thickness were in the order of $1/\text{SNR}$ (or lower), shown as the dotted line in *Figure 5B*. This was also true for a FC of 0.5 mm imaged with an acquired voxel size of $0.31 \text{ mm} \times 0.31 \text{ mm} \times 2.00 \text{ mm}$ at $\theta=40^\circ$. These FCs would likely be obscured, preventing a reliable qualitative assessment of their status. At $\theta=0^\circ$, only the contrast of a FC of 0.5 mm thickness imaged with an acquired voxel size of $0.62 \text{ mm} \times 0.62 \text{ mm} \times 2.00 \text{ mm}$ fell below $1/\text{SNR}$. And indeed, these findings corresponded with what we previously determined from *Figure 3*, and were largely in line with the MRI reader decisions.

Discussion

We investigated the influence of an oblique scan plane orientation in combination with voxel dimensions on FC contrast (i.e., FC intensity relative to the adjacent LRNC) for a typical 2D clinical T1-weighted, black-blood, contrast-enhanced carotid MRI protocol. The use of MRI simulations allowed full scan parameter control and precise knowledge of the plaque geometry, FC thickness, and tissue relaxation times.

Using higher voxel anisotropy or imaging thinner FCs led to a larger influence of scan plane obliquity on FC contrast. The latter is of particular concern because the thinner the FC gets, the more vulnerable the plaque becomes (32). Nevertheless, our simulations showed that the in-plane voxel size and the FC thickness strongly determine FC contrast, and, most interestingly, often outweigh scan plane obliquity for angles up to 40° . FC signal intensity strongly increases if the FC is covered by more voxels when considering out-of-voxel PSF signal spreading. Our findings for different in-plane acquired voxel sizes at no scan plane obliquity ($\theta=0^\circ$) are thus already interesting in and of themselves. We found that, on average, the measured FC thickness increased for increasing θ , as expected from the increase in apparent thickness. An oblique scan plane orientation (or a larger in-plane voxel size) decreases intensity gradients at plaque component interfaces

(blurred edges), which affects segmentation accuracy (33). An elaborate analysis of the overestimation of mm-scale thickness features under scan plane orientation obliquity is given in (28). All FCs with a contrast $<1/\text{SNR}$ were judged by the MRI reader as obscured while all FCs with a contrast $>2/\text{SNR}$ were judged as visible. Out-of-voxel PSF signal spreading caused FC contrast to slightly increase with θ in the cases where $d \geq \delta$. When imaging any FC at an angle with a finite slice thickness δ , the total amount of FC tissue present in the slice (the integral of $\lambda(x)$) increases. If the FC intensity profile would be modeled as the convolution of the $\text{PSF}(x)$ and $\lambda(x)$, one would indeed find a slight increase in peak FC intensity with respect to $\theta=0^\circ$ for the combinations of parameters for which an increase in FC contrast was observed in the MRI simulations. When approaching near isotropic voxels in clinical systems, PSF signal spreading in the slice-select direction or slice overlapping would attenuate this FC intensity enhancement. For clinically applied MRI, alterations in the field-of-view and/or voxel dimensions impact the total scan time and/or SNR (not FC contrast, being a relative measure) according to the SNR equation. An advantage of our methodology was that the simulated images were free of noise, which allows the assessment of FC contrast data reported in our study for arbitrary SNR levels.

Isotropic resolution carotid MR imaging—which is increasingly being used—renders the issue of scan plane obliquity obsolete and it is currently claimed to be favorable for imaging small features (22,23). However, our simulations suggest otherwise: isotropic imaging can actually lead to reduced FC contrast when the FC thickness is less than the PSF width, which is usually the case. Because FC thickness is a predominantly in-plane feature, anisotropic voxels can provide higher FC contrast. While we found that an oblique scan plane orientation reduces FC contrast, we observed that increasing the in-plane resolution (while decreasing the slice thickness) still yielded considerably higher FC contrast even at moderate ($<40^\circ$) scan plane obliquity. This supports the use of anisotropic voxels for FC imaging. In 3D sequences, the number of slice-select phase encoding steps can be lowered to achieve anisotropic imaging, which could also extend to a reduction in scan time and/or noise. We also demonstrated that a properly aligned scan direction at the slice containing the plaque can significantly increase FC contrast, which calls for further investigation into the improvement of scan planning in carotid MRI for FC status assessment in clinical practice, and into the possibility of *a priori* estimation of

FC orientation. Interestingly, our simulations showed that the combination of merely geometrical angulations and finite voxel imaging can obscure even relatively thick FCs (>0.5 mm) in carotid MRI. This obscurement could lead to a false evaluation of FC absence (or thinning) in potentially stable lesions.

A number of assumptions and simplifications were made. Motion artifacts (34) or influences from imperfect blood signal suppression (35), which could contribute to obscuring the FC in addition to scan plane obliquity, were not modeled. Furthermore, a uniform B1 homogeneity was assumed with fixed repetition and echo times in the protocol, and T_1 relaxation times for FC and LRNC tissue were not varied. Note that while these parameters influenced FC contrast equation, they did not affect the relationship with scan plane angle. In the simulations, perfect (uniform) slice excitation was assumed with no influence from other slices (i.e., no cross-talk in case of 2D protocols, or no axial PSF or Gibbs ringing effects in case of 3D protocols). Such effects were not simulated because they are highly protocol-specific. We did not model axial FC morphological variations within a slice. These variations can be substantial, as reported in previous studies (22–24), and should be subject of further investigation. Plaque tissues were modeled as homogeneous, given the large differences in biological structure between FCs and LRNCs (3). A FC is typically well defined in contrast-enhanced MRI as the consequence of different relaxation times of fibrous tissue with gadolinium-uptake and the underlying LRNC (8,9). However, the FC-LRNC interface is not always sharp-edged as assumed in our study. Because the FC thickness measurements were performed on idealized models, those results cannot be directly translated to actual *in vivo* MRI. The advantage of MRI simulations was that we could investigate solely scan plane obliquity without obstructions from any of the aforementioned effects; however, these matters could also influence FC status assessment in practice.

Conclusions

While isotropic-voxel carotid MRI eliminates the issue of scan plane obliqueness, the relatively larger in-plane voxel size could cause FC contrast reduction. In our simulations, a smaller in-plane voxel size at the cost of a larger slice thickness (i.e., voxel anisotropy) often enhanced FC contrast even in the presence of scan plane orientation angles up to 40°. If scan plane orientation obliquity at the slice of

interest is moderate (<40°) or otherwise diminished through careful scan planning, the acquisition of anisotropic voxels could significantly enhance FC contrast which, in effect, could improve the reliability of FC status assessment.

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