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3D black blood MR Angiography of the Carotid Arteries. A simple sequence for plaque hemorrhage and stenosis evaluation

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Abstract

Objectives—To evaluate the diagnostic performance of a new three-dimensional T1-weighted turbo-spin-echo sequence (3D T1-w TSE) compared to 3D contrast-enhanced angiography (CE-MRA) for stenosis measurement and compared to 2D T1-w TSE for intra-plaque hemorrhage (IPH) detection.

Methods—Eighty three patients underwent carotid MRI, using a new elliptic-centric phase encoding T1-weighted 3D TSE sequence in addition to the clinical protocol.

Two observers evaluated image quality, presence of flow artifacts, and presence of intra-plaque hemorrhage, and computed the NASCET degree of stenosis for CE-MRA and for the new sequence. Inter-observer agreement and correlation between 3D TSE and CE-MRA for NASCET stenosis was estimated using Cohen's kappa, and correlation using linear regression and Bland-Altman plots.

Histology was performed on endarterectomy samples for 18 patients. Sensitivity and specificity of 2D and 3D TSE for IPH diagnosis were computed.

Results—3D TSE showed better image quality than 2D TSE ($p < 0.05$). Interobserver agreement was good (kappa 0.86). Correlation between 3D TSE and CE-MRA was excellent ($R = 0.95$) for

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NASCET stenosis. Sensitivity and specificity for IPH diagnosis was 50% and 100% for 2D TSE and 100% and 83% for the 3D TSE.

Conclusions—The new 3D T1-w TSE allows both reliable measures of carotid stenosis, with a slight overestimation compared to CE-MRA (5%), and improved IPH identification, compared to 2D TSE.

Keywords

Atherosclerosis; 3D MRI; Carotid stenosis; Intraplaque Hemorrhage

INTRODUCTION

Degree of carotid stenosis remains the main clinical criteria for predicting the risk of stroke related to atherosclerotic plaque in the carotid bifurcation and therefore it determines the therapeutic or interventional patient management¹. The ability of contrast-enhanced MR Angiography (CE-MRA) to provide accurate measurements of carotid stenoses has been demonstrated². Specific plaque features are also indicators of an increased risk of stroke. Particularly, the presence of intra-plaque hemorrhage is strongly associated with plaque progression^{3,4} and occurrence of cerebrovascular events⁵. A recent meta-analysis study reported that the presence of IPH detected on MRI was associated with a significantly higher risk for event occurrence⁶. The short T1 relaxation time of met-hemoglobin, resulting from the degradation of hemorrhage, led to the development of T1 weighted (T1-w) MRI methods for IPH detection. Cappendijk and colleagues demonstrated the high potential of a gradient echo based sequence (TFE) to detect IPH in the carotid arteries with good inter-rater agreement⁷. Nonetheless, in current clinical practice, a 2D ECG-gated black-blood T1-w turbo spin echo acquisition (2D T1-w TSE) is used for IPH detection⁸. One advantage of TSE type sequences is that when repeated after gadolinium administration, complimentary information can be gained on plaque composition, such as the delineation of the necrotic core and of the fibrous cap. Although a consensus for a precise definition has not been reached in literature, IPH is described as a hyper-intensity, 50% higher than the adjacent muscle tissue.

Recent technical advances in MRI allow the use of three-dimensional (3D) sequences which provide an extended coverage of the investigated anatomical region with improved through plane spatial resolution. When investigating the morphology of the vessel wall, blood signal suppression is necessary. The goal of the present study was to evaluate the IPH detection capability and the correctness of lumen visualization of a new dark blood 3D T1-weighted TSE sequence in comparison with the standard protocol.

MATERIALS AND METHODS

Study population

Eighty three consecutive symptomatic and asymptomatic carotid atherosclerosis patients (64 men, mean age = 68 ± 12 years) referred to the Radiology Department of our hospital for MR plaque evaluation were prospectively included in the study. The inclusion criterion was a carotid plaque thicker than 3 mm detected by ultrasound. Exclusion criteria were prior

carotid stent placement, and any contraindications to MRI (heart pacemaker, metallic implant, severe claustrophobia) or to intravenous administration of gadolinium (pregnancy, allergy, and glomerular filtration rate < 30 mL/min). MR imaging was performed following an informed consent. The study was approved by the review board of our institution.

MRI protocol

All patients underwent the clinical protocol for carotid plaque MRI on a 3T Philips Achieva (Philips Healthcare, Best, The Netherlands). A two element bilateral carotid surface coil (Sense FlexS, Philips Healthcare) was used for image acquisition, positioned on top of the mandibular angles.

Following carotid bifurcation localization, a multiple overlapping thin slab acquisition (MOTSA) time-of-flight (TOF) sequence was performed as follows: repetition time/echo time (TR/TE) 25.0/3.44 ms; flip angle 10°, field of view 180 × 180 × 24 mm, slice thickness 1.6 mm (interpolated to 0.8 mm), in plane resolution 0.45 × 0.45 mm (interpolated to 0.25 × 0.25 mm), 3 signal averages. Subsequently, six axial 2D slices were positioned on the plaque center, perpendicular to the common carotid longitudinal axis, and imaged with an ECG gated double inversion recovery prepared (DIR) spectrally-selective inversion recovery (SPIR) for fat saturation turbo spin echo (TSE) sequence. T1 weighting was obtained using: TR/TE of 1 heartbeat/23 ms, inversion time (TI) 420 ms, field of view 128 × 128 mm, slice thickness 2 mm, in plane resolution 0.45 × 0.45 mm (interpolated to 0.25 × 0.25 mm), bandwidth 289Hz/pixel, 4 averages, parallel imaging (SENSE) acceleration factor: 2 (in the RL direction); echo train length of 9, scan time of 5min 36sec for a heart rate of 60.

The new sequence consisted of a coronal elliptic-centric phase encoding T1-weighted 3D turbo spin-echo (TSE) with the following parameters: TR/TE 700/50 ms, voxel 0.63 mm isotropic (interpolated to 0.4 × 0.4 × 0.63 mm), echo train length of 20, partial Fourier factor of 0.6, non-volume selective excitation, TSE echo spacing/shot duration 6.8/162 ms, pseudo-steady state (PSS) refocusing control consisted of an initial non-linear decrease from 128° to 40° (4 startup echoes) followed by a non-linear increase to 120° (5 echoes) and a linear increase to 160° for the remainder of the echo train, acquisition bandwidth (BW) 827Hz/pixel, NA 1, scan time of 4 min. The sequence relies on de-phasing of flowing spins in the echo train length, inherent to TSE acquisitions. Furthermore, three dummy echoes were added before the TSE acquisition in order to crush the flowing spins signal for the center of k-space, since phase ordering is centric.

Contrast-enhanced MRA (CE-MRA) coronal images were obtained with a 3D T1-GRE sequence using the contrast-enhanced timing-robust angiography (CENTRA) technique and the following parameters: TR/TE 4.5/1.7 ms, field of view 320 × 320 × 75 mm, 150 slices of 1 mm (interpolated to 0.5 mm), in-plane resolution: 0.63 × 0.63 (interpolated to 0.5 × 0.5 mm), parallel imaging (SENSE) acceleration factor: 2 (in the RL direction); time to center of k-space: 2.5 s, scan time of 1 min 10 sec. The acquisition was performed during first pass of 30 cc of a Gadolinium-based contrast agent (DOTAREM©, Guerbet, France), administered at 2 cc/s, followed by a 10 cc saline flush. Total acquisition time did not exceed one hour.

Image Quality

Image quality in terms of motion artifacts and noise level on each sequence was evaluated by two experienced observers in an independent manner, using a 5-point scale as follows: (0) Not assessable – strong motion artifacts preventing vessel wall delineation; (1) Poor – motion artifacts, but visible vessel wall, with high noise preventing analysis, (2) Moderate – visible vessel wall but high noise level, (3) Good – moderate noise, (4) Excellent – absence of motion artifacts and noise. Acquisitions with a score of 0 or 1 were excluded from the analysis. Furthermore, when a complete dataset was not available for a patient, the entire exam was excluded from the study.

Additionally, presence of flow artifacts (plaque mimicking artifacts) and sharpness of vessel wall depiction were assessed only on the T1-weighted 2D and axial reformatted 3D TSE. Flow artifacts, defined as intraluminal iso-intense signal not visible of the CE-MRA, were rated as: 0: Strong, 1: Moderate, 2: Absent. Sharpness of vessel wall was rated as: 0: Poor, 1: Moderate, 2: Good.

Degree of stenosis

Evaluation of the degree of stenosis using the NASCET criteria was performed for both the Gd enhanced MRA and the 3D TSE sequence. For this, multi-planar reformatting (MPR) was performed perpendicular to the vessel's long axis at different locations in order to measure the diameter of the vessel in the narrowest point of the stenosis ($\phi_{stenosis}$), when a stenosis was present, and in a segment considered healthy upstream from the stenosis (ϕ_{normal}). The diameter of the vessel was measured on each MPR generated image and the degree of stenosis was then calculated using the NASCET criteria⁹.

IPH detection

Presence of intra-plaque hemorrhage (IPH) was qualitatively defined as a hyper-intense signal with reference to the immediately adjacent sternocleidomastoid, a well-described methodology¹⁰ independently on the 2D T1-w TSE and then on the 3D T1-w TSE. A score of 1 or 0 was given for the entire plaque when IPH was deemed present or absent.

Histological Analysis

A subgroup of 18 patients underwent carotid endarterectomy based on the following criteria: NASCET stenosis $\geq 50\%$ if symptomatic and NASCET stenosis $> 70\%$ if non-symptomatic. The excised plaque was fixed in formalin, decalcified, and embedded in paraffin. Transverse sections were performed across the entire length of the endarterectomy specimen at 2 mm intervals. Six to 8 adjacent 5- μm transverse sections were taken from each paraffin block. Each section was stained with hematoxylin and eosin (H&E). Examination of all histology sections was performed by a researcher experienced in vascular pathology and blinded to the imaging results. Similarly to the image based IPH detection, a score of 1 or 0 score was given for the entire plaque depending on whether IPH was deemed present or absent. IPH was identified by the presence of relatively intact red blood cells with a polymorphonuclear infiltrate. A slice by slice quantification of hemorrhage was not performed because this component is generally difficult to contour manually from the lipid rich core.

Statistical analysis

Inter-observer agreement for image quality assessment and for qualitative IPH detection on MR images was estimated using quadratic weighted Cohen's kappa. Nonparametric bootstrap was used to calculate 95% confidence intervals for kappa estimates. Image quality scores were compared using a Wilcoxon signed rank test. Inter-observer agreement for NASCET degree of stenosis measurement was assessed using the intra-class coefficient of correlation (ICC). Correlation for NASCET stenosis measurements between CE-MRA and 3D T1-w TSE was evaluated using linear regression and Bland-Altman analysis.

Agreement between the 2D T1-w, the 3D T1-w TSE, and histology in IPH detection was evaluated by computing the phi correlation coefficient.

Statistical analysis was performed using R (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <http://www.R-project.org/>). Values are given as mean \pm standard deviation (SD). A p value < 0.05 was considered to indicate statistical significance.

RESULTS

Out of the total eighty three patients that underwent the MRI protocol, fourteen patients were excluded from further analysis due to presence of image artifacts (image quality score < 2 for the 2D sequence in 5 patients and for the 3D-TSE sequence in 6 patients, and for the TOF in 3 patients) and eight patients for incomplete exam. A total of 61 patients were included in the analysis.

Very good inter-observer agreement was obtained for image quality assessment (kappa = 0.96 (CI 0.9, 0.99) for 2D T1-w TSE (median score = 3.25) and 0.83 (CI 0.54, 0.99) for 3D T1-w TSE (median score = 4), $p < 0.001$). Excellent agreement was obtained for assessment of flow artefacts (kappa = 1 (CI 1, 1) on 2D images (median score = 1) and 0.98 (CI 0.92, 1) on 3D images (median score = 1), $p < 0.001$), and for assessment of wall sharpness (kappa = 0.94 (CI 0.83, 1) for both 2D (median score = 2) and 0.93 (CI 0.81, 1) for 3D (median score = 2), $p < 0.001$). Overall, 3D T1-w TSE showed reduced motion artifacts ($p = 0.001$) and reduced flow artifacts ($p < 0.005$) in comparison with 2D T1-w TSE. No significant difference was found for the sharpness of the vessel wall ($p = 0.05$).

Degree of stenosis

Stenoses were identified in 76 carotid arteries for which the NASCET degree of stenosis was computed for both 3D T1-w TSE and CE-MRA. Agreement between observers was excellent with an ICC of 0.997 for both sequences. Correlation between 3D T1-w TSE and CE-MRA was excellent ($R = 0.95$) despite a trend for 3D T1-W TSE to overestimate it (5.2%; (CI 3.5 to 7%)) (Figure 1).

IPH detection

Representative images of a hemorrhage positive plaque acquired using the standard protocol, 2D T1-w TSE, and with the new 3D T1-w TSE sequence, for the same patient are presented in Figure 2. Luminal geometry is similar between the bright blood MRA and the black-blood

3D TSE (Figure 3). Furthermore, the intra-plaque hemorrhage signal is stronger in the 3D TSE image compared to the corresponding 2D TSE cross-section (Figure 4) probably due to stronger T1 weighting of the 3D TSE sequence.

Fair inter-observer agreement was obtained for qualitative detection of IPH for 2D T1-w TSE ($\kappa = 0.6$) and good agreement was obtained for 3D T1-w TSE ($\kappa = 0.72$). These findings are supported by the results of the comparison with histological data, when this data was available (18 patients). Agreement between histology findings and imaging for IPH detection was 0.88 (CI 0.7, 0.95) with the 3D T1-w TSE and it was 0.57 (CI 0.13, 0.82) with the standard protocol. Sensitivity and specificity for IPH diagnosis was 58% (7/12) and 100% (6/6) for the standard protocol and 100% (12/12) and 83% (5/6) for the 3D T1-w TSE sequence using histology as the gold standard. Representative MRI and histological images are presented in Figure 5.

DISCUSSION

The degree of luminal stenosis and presence of IPH are the two major criteria predicting stroke in patients with extra cranial carotid stenosis. We demonstrated the ability of a single MRI scan to evaluate these two parameters in a reliable manner compared to the standard protocol, 2D T1w-TSE, TOF, and CE-MRA. Furthermore, this is a simple sequence, performed with a short acquisition time (4 min) and does not require contrast agent injection. The sequence has a large coverage, particularly interesting for extended and multi-focal atherosclerotic plaques that can sometimes be missed by the standard 2D sequence.

Carotid artery IPH detection using a T1 weighted 2D ECG-gated sequence is a relatively lengthy acquisition (>5 min) and thus may result in poor image quality due to patient motion. In our study we excluded fourteen patients (17%) because of un-diagnostic image quality. Previous studies in agreement with our experience reported high percentages of un-diagnostic studies¹¹. The new 3D TSE sequence had overall higher image quality scores, indicating its superiority to the other standard sequences, probably owing to a shorter acquisition time (~4 minutes).

Carotid artery luminal assessment is the key element in clinical decision making for patients with carotid stenosis. DSA has historically been the gold standard in the evaluation of carotid stenosis. However, the diagnostic role of DSA has progressively been replaced by less-invasive modalities, like CTA and MRA, both techniques requiring contrast injection¹². Despite numerous published studies, there is no consensus regarding the indications for a preferred use of CTA over MRA. Excellent and robust sensitivities and specificities have been reported for both techniques in distinguishing <70% and >70% ICA stenosis^{13,14}. In the present study, we have used CE-MRA as the gold standard for stenosis evaluation. The new sequence compared favorably with the gold standard.

IPH identification using MRI has been widely described. Owing to the short T1 relaxation time of hemorrhage, T1 weighted MR sequences have been developed for the detection of IPH. Thus, the majority of studies describe IPH as a hyper-intense signal in the carotid plaque compared with the normal vessel wall or the sternocleidomastoid muscle on one T1

weighted sequence or on a combination of several sequences (TOF, T1-w, Proton Density). The standard ECG-gated 2D T1-w sequence has a relatively long repetition time, around 1000 ms, depending on the patient's heart rate, and thus a suboptimal T1 weighting for IPH detection. Boussel et al have proposed a modification of this sequence that reduced the effective TR of the sequence, thus resulting in an improved T1 weighting¹⁵. Similarly, the shorter TR (700 ms) of our 3D TSE approach improves the T1-weighting and the contrast of IPH. The higher sensitivity obtained with histology as a gold standard indicates that 3D T1-w TSE has superior contrast for IPH detection.

Recent technical advances in MRI enabled the use of three-dimensional (3D) black blood sequences which have the potential to provide both stenosis measurements and plaque characterization. The potential of TSE type sequences to assess the vascular lumen has been demonstrated recently by Mihai et al. who found that the 3D T2-weighted SPACE sequence provided accurate measurements of degree of stenosis and lumen size¹⁶. However, T1-weighted signal is needed for IPH detection. 3D T1-weighted gradient echo (GRE) acquisitions were demonstrated previously for IPH detection^{17,18}. Balu and colleagues achieved good blood signal suppression with a rapid 3D GRE sequence by adding a Motion-Sensitized Driven Equilibrium (MSDE) preparation before the fat saturation pulse preceding the centric encoded readout¹⁹. Another 3D GRE based sequence, SNAP, appears very promising in the detection of IPH²⁰. Furthermore, this sequence simultaneously generates bright-blood angiography images that allow measurement of degree of stenosis, for an acquisition time of 5 minutes and 0.8 mm isotropic resolution. Our TSE sequence allowed a higher spatial resolution at acquisition (0.63 mm) particularly important when imaging atherosclerotic plaques. Furthermore, compared to these GRE based sequences, the suppression of the blood signal is inherent for our sequence since it is a 3D turbo spin echo (3D TSE). Furthermore, three dummy echoes were used with our 3D-TSE sequence to further reduce the signal from blood. The number of dummy echoes could be slightly increased to further reduce blood signal, but this approach will also reduce the signal of the static tissue, ie the vessel wall signal. We found that three dummy echoes offered a good compromise between blood suppression and overall SNR.

Current surgical guidelines are under debate, particularly on what concerns asymptomatic stenoses¹. With the advent of novel medical therapies, the risk of stroke at 5 years for asymptomatic lesions is equivalent for surgical and pharmaceutical treatment²¹. It appears necessary to identify patient subgroups at high risk of stroke that could benefit from more aggressive therapies. The ECST-2 trial (Stroke Research Group Institute of Neurology, University College London), currently in the recruitment phase, will compare, for symptomatic and asymptomatic moderate to severe carotid stenoses, the risks and benefits between two treatment options: optimized medical therapy (OMT) alone or an association of OMT and an invasive treatment: endarterectomy or stenting. Similar comparisons will be performed in the SPACE-II trial with two important differences: one is that the invasive procedures are distinctly evaluated in association with best medical therapy, and the other that the inclusion criteria is asymptomatic stenosis of more than 70%²². In the context of this type of multicenter trials, our 3D TSE sequence appears interesting as it provides reliable stenosis measurements and IPH detection, is easy to set up, has a relatively short acquisition time, and does not require contrast agent administration.

The limitation of our study is that no direct comparisons were performed with other 3D T1-w sequences. However, these sequences were not available at our institution. Another potential limitation is that the histological analysis was not performed for all subjects. This is justified by the fact that there was not a clinical indication for surgical intervention for the rest of the subjects. Another limitation may be related to the fact that we did not perform a slice by slice comparison between histology and MRI which could provide an assessment of the IPH size. However, because of averaging in MRI a slice by slice comparison is very difficult and was beyond the scope of the current paper. Finally, dedicated carotid coils were not used in this study. Nonetheless, the image quality obtained with the use of the flexS coils was sufficient to demonstrate correct identification of IPH. The use of dedicated carotid coils is expected to improve image quality by an increase in SNR.

In conclusion, we presented here a simple 3D T1 weighted black blood angiography sequence that allows reliable stenosis evaluation as compared to CE-MRA and IPH identification as demonstrated by the excellent agreement with histological findings.

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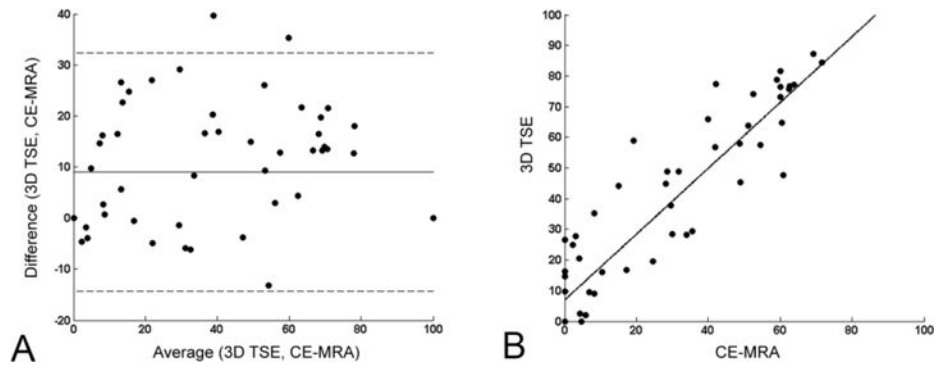


Figure 1. Agreement for NASCET degree of stenosis measurements between the new 3D-T1 sequence and the standard CE-MRA. The correlation plot (left) shows a very good correlation ($R=0.94$) and an offset of 5% for the 3D-T1 measurements as observed in the Bland Altman plot (right).

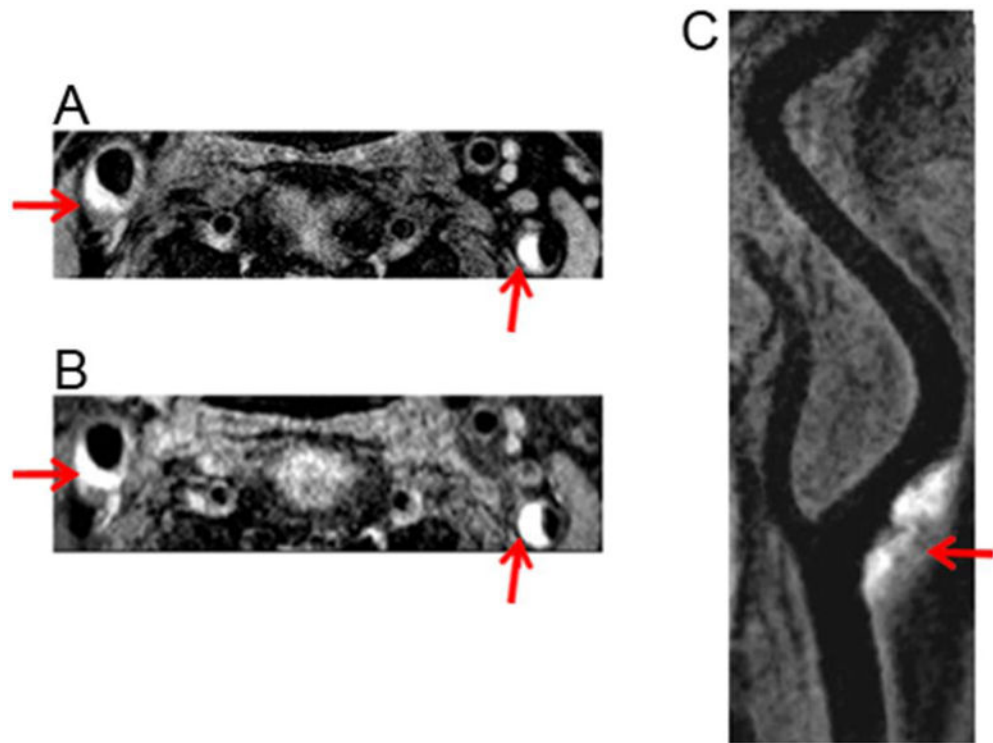


Figure 2. Representative images of hemorrhagic plaques acquired with the 2D T1-w TSE (A) and with the 3D T1-w TSE: transverse MPR (B) and oblique MinIP (C, the right carotid bifurcation). Bilateral hyperintense signal can be observed on both sequences indicating presence of IPH (red arrows). The 3D T1-w sequence depicts the extent of the lesion and of the luminal stenosis (<50% NASCET)

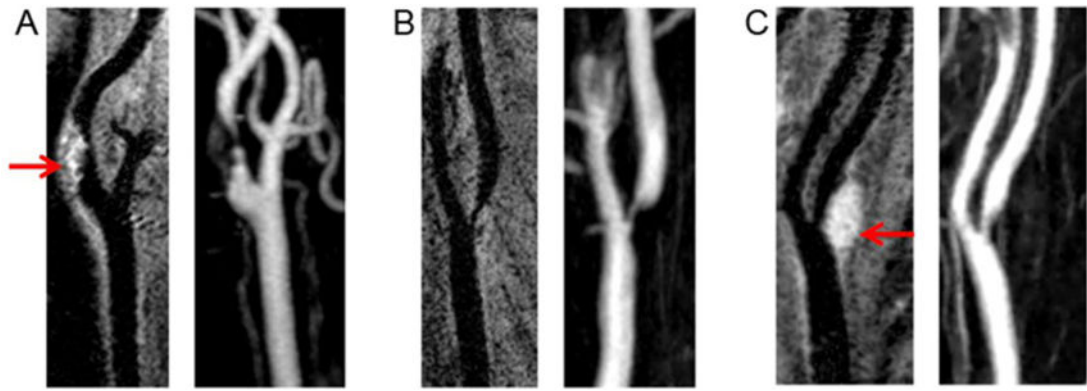


Figure 3.

Three patients with internal carotid stenosis: 3D T1-w TSE MinIP reconstructions (left on

A, B and C) and standard CE-MRA MIP reconstructions (right on A, B and C).

Hyperintensity of the plaque (red arrows) is clearly visible with the 3D T1-w TSE sequence (A and C) suggesting IPH.

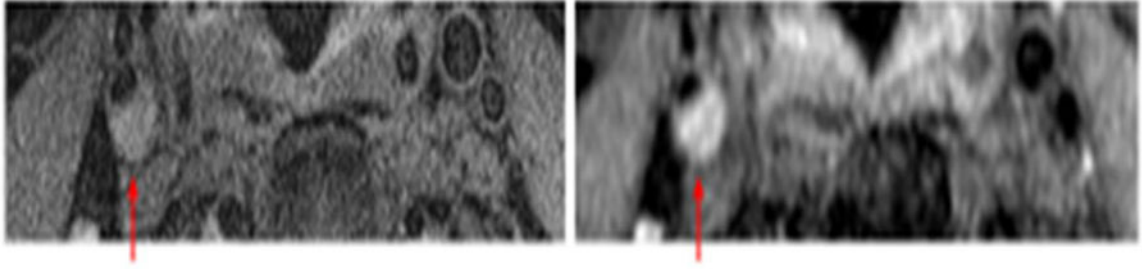


Figure 4.

Comparison of transverse images of an atherosclerotic plaque in the right internal carotid artery acquired with the 2D T1-w TSE (left) and the 3D T1-w TSE (right). A hyperintense signal can be observed on the 3D T1-w sequence. However, the signal was relatively isointense with respect to the sternocleidomastoid muscle on the corresponding image acquired with the 2D sequence and was not considered as indicated IPH.

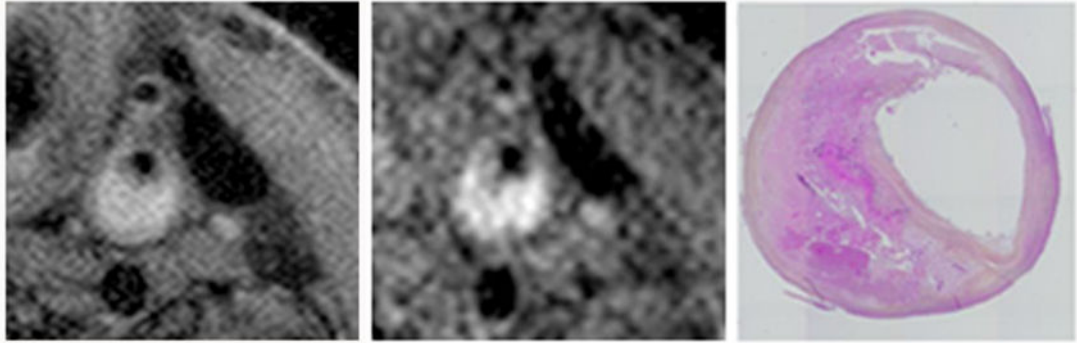


Figure 5.

Transverse MRI images acquired with the 2D T1-w sequence (left) and the 3D T1-w sequence (center) and the corresponding histological slide with H&E staining (right). Both MR images indicate IPH which was validated by histology.