Diagnostic impact of T2* MRI imaging for improved ex vivo classification of complicated plaques

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Introduction: Next to atrial fibrillation and aortic atherosclerosis high-grade ICA stenoses constitute a leading source of ischemic stroke induced by intraplaque hemorrhage, plaque rupture and consecutive thromboembolism. Especially complicated plaques classified as type VI following the American Heart Association (AHA classification) contain thrombi, acute or old intraplaque hemorrhage and/or ulceration of the fibrous cap. In various in-vivo and in-vitro studies, non-invasive high spatial resolution MRI has proven to be a valuable tool in the characterization of carotid plaque composition. However, previous studies based on T1, T2, proton density and diffusion weighted imaging protocols for tissue identification in comparison to histology specimen and T2* sequences have not been used for the characterization of plaque hemorrhage in-vivo or ex-vivo at 9.4T. Based on these protocols, sensitivity for the detection of intraplaque hemorrhage varied between 71-91 % and showed limited inter-rater agreement and specifity (1-3). Thus, it was the purpose of this study to evaluate an optimized MRI protocol including T2*-weighted GRE-imaging in combination with established sequences using ultra-high field MRI (9.4T) for improved identification of plaque bleeding and intraluminal thrombi.

Methods: Plaque specimen of 38 individuals (52.6% symptomatic, 47.6% asymptomatic stenosis) undergoing carotid endarterectomy for ICA stenosis ≥70% (ECST criteria, local degree of stenosis) were fixed in 4% formalin immediately after surgical resection and evaluated at a high field 9.4T MRI system (Bruker BioSpin 94/20, Ettlingen, Germany).
The MRI protocol included 3D imaging with different contrasts and a resolution of ~100µm^3: T1±fatsat GRE imaging: TE = 2.9ms, TR = 13.4ms, flip angle =20° and 18 averages. T2* GRE imaging: TE = 7.9ms, TR = 12.8ms, flip angle =10° and 10 averages. T2 SE imaging: TE = 45ms, TR = 3000ms, flip angle = 90°/180°, turbo factor = 8. In addition, 2D multi-slice diffusion-weighted SE-EPI was performed with 150 x 200µm in-plane resolution and 400µm slice thickness: TE = 40ms, TR = 6750ms, 2 A0-images, 6 different b-values (100, 200, 400, 600, 800, 1000 s/mm^2) and 6 directions. Parametric Signal Intensity (SI), Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA) maps were calculated from diffusion weighted images. Data acquisition was performed with about 10 hour duration of total scanning time. Histology was used as the reference standard. From the 38 resected plaques, 153 coronal paraffin slices were prepared and 54 were evaluated to date. Standard Hämatoxilin (HE) and Elastica-van-Gieson (EvG) staining were used for tissue component definition.
In consensus reading of two readers plaques were screened for the presence of calcification, acute or old intraplaque hemorrhage, lipid rich/necrotic core (LR/NC), loose matrix, fibrous tissue or intraluminal thrombus. Plaque classification was based on simultaneously presented, T1, T2*, T2 and diffusion images. Sensitivity and specificity of MRI compared to histology were calculated for each component. Readers of MRI data were blinded to results of histological examination and vice versa. Furthermore, based on plaque components AHA classification was additionally performed with slight modification for MRI and histological data as previously described (1).

Results: An example of the appearance of older intraplaque hemorrhage in T2* compared to T1 is given in Figure 1. In contrast, characteristics of an acute bleeding and intraluminal thrombus are presented in Figure 2. Sensitivity and specificity of MRI are summarized in Table 1 demonstrating high sensitivity of MRI for the detection of acute and old plaque hemorrhage and a moderate sensitivity but very high specificity for the identification of the LR/NC. AHA classification using MRI data was correct in 51/54 cases (94.4%) when compared with the classification based on histological examination as the reference method.

Discussion: Our initial findings show the accuracy of our ultra-high field MRI protocol for the reliable characterization of plaques ex vivo. Both the sensitivity for the detection of calcification, acute and older intraplaque bleeding and the accuracy of AHA classification were high. The currently low sensitivity for the identification of thrombi might be due to the relatively low frequency of this pathology and the resulting high error in case of false negative detection in MRI. Our findings suggest that the additional application of T2* sequences provides high sensitivity for the detection of bleedings and in particular the differentiation of acute and old bleeding. The precise differentiation of acute and old bleeding might be of clinical relevance as the risk of plaque rupture and cerebral embolism is higher in case of acute hemorrhage, especially if the bleeding is located superficially. Furthermore, use of T2* allowed for the precise differentiation between acute bleeding and plaque necrosis which are both hyperintense in T1 weighted imaging but show markedly different signal in T2* (necrosis=bright signal, bleeding=low signal as in figure 2D).As a result, our imaging protocol improved the identification of the clinically important complicated plaque AHA type VI showing hemorrhage as the most characteristic feature. Future studies evaluating the additional impact of T2* in patients with high-grade ICA stenosis in-vivo are needed to define the prognostic impact of such improved plaque characterization for future primary and secondary prevention in patients with ICA stenosis.

References: (1) Clarke et al. Stroke, 2006;37;93-97 (2) Shinnar et al. Arterioscler Thromb Vasc Biol 1999;19:2756–2761. (3) Chu et al. Stroke 2004;35;1079-1084.

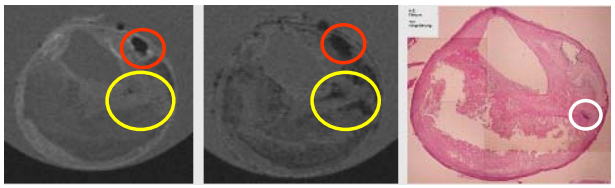

Figure 1: T1 (left), T2* (middle) imaging and histological specimen examination (right), 10 x amplification, HE staining. In contrast to T1 imaging intra-plaque hemorrhage can be appreciated more clearly in the T2*-weighted image (hypointens signal, encircled yellow). The corresponding older bleeding is indicated in the histology section by the white encircled purple staining. Furthermore, calcification presents as clearly demarcated hypointensity of the same size in T1 and T2* imaging (encircled red).

Detected tissue components N = 54 plaque slices	Sensitivity (%)	Specificity (%)
Acute hemorrhage (n = 44)	90.1	70.0
Old hemorrhage (n = 44)	93.2	60.0
Calcification (n = 38)	92.1	62.5
LR/NC (n = 26)	73.1	96.4
Thrombus (n = 6)	50.0	100.0
Fibrous tissue (n = 52)	84.6	50.0
Loose matrix (n = 32)	87.5	72.7

Table 1. Sensitivity and specifity for the identification of plaque components using multi-contrast MR imaging in comparison with histological examination as the reference method. LR/NC = lipid rich/necrotic core. Note that both the number of thrombi and of plaques without old or acute hemorrhage was relatively small.

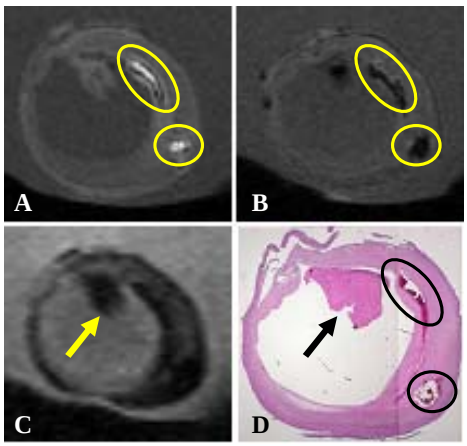

Figure 2 T1 (**A**), T2* (**B**) and diffusion (**C**) weighted imaging for the detection of acute bleeding and intraluminal thrombus. (**D**): histological specimen (10 x amplification, EvG staining). In contrast to old hemorrhage (Figure 1) acute bleeding shows clear hyperintensity in T1 and complementary hypointensity in T2* (yellow encircled in **A** and **B**), histological reference black encircled in **D**. Further, a thrombus can be best identified on diffusion weighted images as intraluminal hypointense structure (yellow arrow in **C**). The almost isointense signal in T1 (**A**) and hyperintense signal in T2* (**B**) suggest the assumption of an older thrombus. **D**: Histological examination shows a thrombus (black arrow) predominantly being composed of fibrin.