In-vivo lipid quantification in carotid plaques using multi-slice T2 mapping: histological validation

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Introduction Carotid plaque morphology and composition play an important role in the origin of cerebral ischemic events[1] and MRI is the most promising non-invasive tool for identifying features of plaque vulnerability such as the lipid core size[2]. Nevertheless, the current standard technique (multicontrast MRI) requires contrast media and post-acquisition interpretation, and can only detect large coalescent pools of lipid. Additionally, multicontrast MRI is affected by image intensity variations and suffers from blurring artefacts that affect plaque characterization[3]. Quantitative T2 mapping has recently emerged as a promising alternative because it can measure plaque MR properties directly on a voxel by voxel basis and can discriminate between the lipid core and the surrounding fibrous tissue[4]. In-vivo vascular MRI has long aspired to assess plaque lipid content in a direct and objective way that can be standardized among different systems for use in multicentre studies. The purpose of this in-vivo study was to develop a multi-slice T2 mapping method for plaque lipid quantification and validate it against histology in endarterectomy patients.

Methods Pulse sequence: We combined a novel black-blood technique based on non-selective Delay Alternating with Nutation for Tailored Excitation (DANTE) pulse trains[5] with a chemical-shift-selective fat saturated multiecho spin-echo (MESE) sequence to acquire 5 slices with 14 echoes in ~4 min. Acquisition parameters: TR = 2000 ms, TE = 9-127 ms, partial Fourier = 5/8, FOV = 128 × 128 mm, matrix size = 384 × 384, slice thickness = 2 mm, slice gap = 2 mm. DANTE parameters: FA = 8°, number of pulses = 120, interval between pulses = 0.5 ms, Gz = 18 mT/m and gradient duration = 0.4 ms.
In-vivo MRI: 40 patients scheduled for carotid endarterectomy (50-99% carotid stenosis on Ultrasound), either symptomatic or asymptomatic, were imaged at 3T (Siemens Verio) max 24 hours before surgery (IRB approved, written consent obtained). We acquired the standard multicontrast MRI and our DANTE-MESE sequence using a 4-channel carotid coil (Machnet). T2 maps of the carotid arteries were generated using mono-exponential nonlinear fitting[4], and the lumen and external vessel boundary were segmented using a semi-automated procedure[4]. Lipid core without haemorrhage has shorter T2 than normal vessel wall and fibrous tissue, whereas intraplaque haemorrhage infiltrating the lipid core yields longer T2 than all other plaque components[4]. In order to account for both components of the plaque lipid core, optimal lipid segmentation was achieved by the combination of T2 threshold values that produced the highest correlation and lowest RMSE calculated using leave-one-out cross-validation against histology.
Histology: Plaques were freshly collected at the time of carotid endarterectomy and divided at the point of maximal stenosis into 2 halves: one half was formalin-fixed, decalcified, and processed into a paraffin block; the other half was snap-frozen in OCT (Optimal Cutting Temperature medium). 5 µm (for paraffin) and 10 µm (for OCT frozen) tissue sections were cut at 1mm intervals using the carotid bifurcation as an anatomical landmark in order to match locations with T1w images as a reference. Haematoxylin and eosin (H&E), as well as Masson Trichrome, staining were performed for plaque morphology. Selected frozen sections were post-fixed with formalin and stained with Oil-red-O to confirm the lipid content and distribution (Fig. 1). Plaque lipid was manually segmented on high-resolution histological images and percentage lipid cross-sectional area was then calculated.

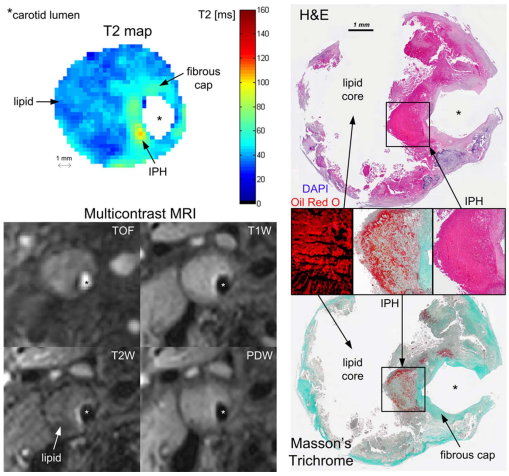

Figure 1: Plaque T2 map, multicontrast MRI and histology.

Results 14 out of 40 patient MRI datasets were rejected due to strong motion artefacts. 26 plaques (60 slices in total) had sufficient image quality and matching histology (Fig. 1, median age 69, range 43 - 90, male/female = 3.2). T2 threshold values of 42 and 90 ms represented the global optimum by achieving the highest correlation r = 0.85 and lowest RMSE = 10.5% against histology (Fig. 2, $p < 0.0001$). To investigate the potential clinical application of in-vivo plaque T2 mapping, we compared symptomatic (n = 15, median age 73, stenosis on Ultrasound = 80 ± 9%) and asymptomatic (n = 11, median age 60, stenosis = 83 ± 9%) patients and found that symptomatic plaques contained significantly more lipid than asymptomatic plaques (Fig. 3A, p = 0.006). We also performed an ROC analysis and calculated a fair/good ability to discriminate between the two groups (AUC = 0.79, p = 0.012). In the literature a large lipid core has been defined as >25% of the cross-sectional plaque area[1]. This value was therefore used as a cut-off for the lipid area in order to classify plaques as symptomatic or asymptomatic (Fig. 3B, χ^2 test p = 0.0033, sensitivity = 67%, specificity = 91%).

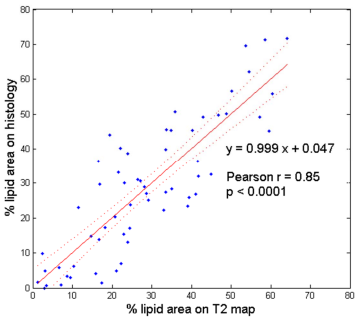

Figure 2: Lipid area on T2 maps vs. histology.

Discussion We have demonstrated that in-vivo lipid quantification by multi-slice T2 mapping is strongly correlated with histology and can discriminate between symptomatic and asymptomatic plaques, and hence has a lot of potential for clinical application. However, this carotid MRI study has also highlighted the limitations of the DANTE-MESE sequence, which is strongly affected by patient motion due to the long acquisition time. Although patients were instructed not to move during acquisition and their head movements were limited by the head holder, swallowing and heavy breathing caused artefacts in 35% of the patients, which were excluded from the analysis. In order to use our technique in clinical trials for patient stratification and drug development it will thus be necessary to improve its robustness and reliability by developing and implementing an effective motion correction strategy. In Fig. 3B the low sensitivity due to the number of false negatives can be explained by the fact that a small lipid core <25% is not sufficient to guarantee the stability of the plaque. On the other hand, the high specificity is particularly encouraging as it agrees with the results found in the literature regarding the strong association between large lipid core >25% and higher risk of plaque rupture[1].

Conclusion For the first time, we have validated in-vivo multi-slice T2 mapping against histology, demonstrated its ability to quantify plaque lipid content and to classify plaques as symptomatic or asymptomatic based on their lipid core size. This technique can potentially be used to identify patients at risk of plaque rupture, stratify for more intensive lipid treatment and monitor response to treatment in clinical trials.

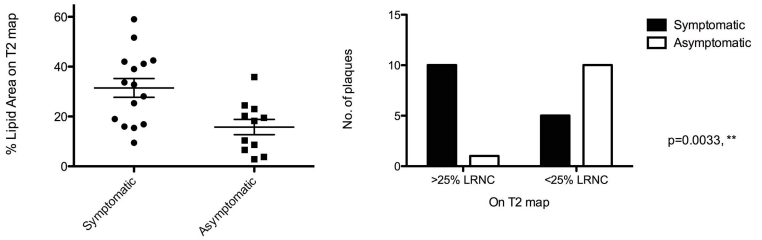

Figure 3: Symptomatic vs. asymptomatic plaques. (A) Lipid content difference (p = 0.006) and (B) classification using 25% as cut-off for large lipid-rich necrotic core (LRNC).

References [1] Redgrave J *et al.* Circ: 113, 2320–2328 (2006). [2] Cai J *et al.* Circ: 112, 3437–3444 (2005). [3] Biasiolli L *et al.* JMRI: 33, 1136–1143 (2011). [4] Biasiolli L *et al.* JCMR: 15, 69 (2013). [5] Li L *et al.* MRM: 68, 1423–1438 (2012).