OPTIMIZED THRESHOLD SELECTION FOR AUTOMATIC CAROTID INTRAPLAQUE HEMORRHAGE DETECTION IN MAGNETIZATION-PREPARED RAPID ACQUISITION GRADIENT-ECHO (MP-RAGE) MRI WITH HISTOLOGY VALIDATION

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Introduction: Intraplaque hemorrhage (IPH) is a critical factor in atherosclerotic plaque progression and destabilization [1]. IPH can be identified as hyperintense regions compared to surrounding tissue on highly T1-weighted sequences such as MP-RAGE [2,3]. Other studies have used thresholds (e.g. 150% or 200% of adjacent muscles signals) to determine hyperintensity [4,5]. However, to our knowledge, studies to determine optimum objective criteria for IPH detection with MP-RAGE are lacking. Identification of an MPRAGE hyperintensity threshold that corresponds to IPH areas verified on histology is needed, which will ultimately allow automated techniques for IPH detection and quantification.

Aims 1) To determine an optimized threshold for carotid IPH detection on MP-RAGE images using matched histology specimens as the gold-standard; 2) To automatically detect carotid IPH on MPRAGE MRI.

Materials and Methods: Subjects: After obtaining IRB-approved consent, 14 patients scheduled for carotid endarterectomy (CEA) were recruited for this study. MR Imaging: Before CEA surgery, patients were imaged on a GE Signa 3.0T MR scanner using a four-channel phased-array carotid coil (Pathway MRI, Seattle, WA). An optimized 3D MP-RAGE sequence [6] was used (TR/TE=13.2ms/3.2ms, spatial resolution: 0.63×0.63×1mm). Histology: Carotid endarterectomy specimens were processed and matched to axial MR, resulting in 133 matched slices from 14 patients. IPH was outlined by a trained pathologist blinded to MRI findings. Presence/absence, and area of IPH were noted. Image and Data Analysis: Carotid outer wall boundaries were drawn by trained reviewers. In order to reduce the effect of signal inhomogeneity associated with the surface coil, Regions of Interests (ROIs), centered on the carotid artery with a radius of 2cm were selected in each slice (Figure 1.a). Three kinds of signal intensity references were selected: the mean value of the sternocleidomastoid muscle (SCM) within the ROI (manually selected); the mean value of adjacent soft tissue (AST) (manually selected as areas with isointensity as the fibrous tissue in the artery); and the median value (MED) within the automatically generated ROI. AST by virtue of its proximity to the carotid may provide a better reference than SCM which is closer to the skin surface and may be biased towards a higher value relative to the carotid artery due to the surface coil sensitivity. Ratios of the signal intensity of each pixel within the vessel wall and corresponding reference intensities (SCM, AST or MED) within the same slice were calculated to produce relative values more comparable between slices and subjects. For each reference, the area under the curve (AUC) was computed to summarize overall IPH detection performance. Different threshold values were tested to determine the sensitivity, specificity, and Pearson's correlation coefficient between IPH areas measured in MRI and those in histology specimens. Area ratios (ratios of MRI identified IPH areas to histology identified IPH areas) were also calculated, using linear regression without intercept. Bootstrapping was used to calculate the confidence interval for each statistical parameter. In addition to the complete data set, subsets of data created by excluding slices [3] with heavily calcified IPH (>50% IPH area calcified), or IPH areas smaller than a cutoff area were examined.

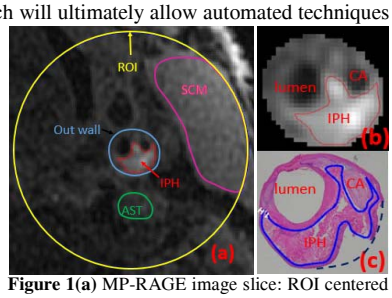

Figure 1(a) MP-RAGE image slice: ROI centered on the carotid artery with a radius of 2mm; SCM, sternocleidomastoid muscle; AST, adjacent soft tissue **(b)** Enlarged artery area from (a) with IPH contour detected using 200% of MED as reference **(c)** Matched histology specimen with IPH outlined (specimen deformed after processing, dashed line shows the original form).

Results: 8 of the 133 slices were excluded when the SCM was used as reference, since the SCM was more than 2cm away from the artery in those slices. Automatic IPH identification using threshold based on MED compared well with histology identified IPH (an example is shown in Fig 1). Optimized thresholds to detect the presence of IPH were determined by maximizing Youden's Index (sensitivity+specificity-1), and were summarized in Table 1. Optimized thresholds did not vary significantly with different data subsets, while the sum of specificity and sensitivity, AUC and Pearson's correlation coefficient (r) increased when heavily calcified IPH and/or IPH smaller than cutoff area was excluded. This was likely because 1) co-localized calcification lowered the signal intensity and 2) the small IPH areas were below or close to the resolution of MP-RAGE. Pearson's correlation coefficients (r), ratios of IPH area measured in MRI and histology (area ratio), sensitivity and specificity for various thresholds using the AST and MED as reference were shown in Figure 2.

Table 1. Performance of optimized thresholds based on three different references

Data subset			Optimized threshold (95% confidence interval) (%)***			Sensitivity, specificity (%)			Area Under the Curve (95% confidence interval)			Pearson's correlation coefficient (r)		
IPH Area(mm^2)*		n+/n**	SCM	AST	MED	SCM	AST	MED	SCM	AST	MED	SCM	AST	MED
	>0	63/133	100(73,131)	162(115,208)	223(197,275)	51,81	46,88	51,80	0.69(0.53,0.83)	0.71(0.55,0.86)	0.58(0.42,0.75)	0.62	0.84	0.81
	>1.25	52/122	101	162	223	57,82	54,87	60,80	0.71(0.56,0.87)	0.72(0.56,0.84)	0.64(0.45,0.80)	0.62	0.84	0.81
	>2.80	34/104	104	160	223	57,84	68,84	68,80	0.74(0.64,0.91)	0.79(0.55,0.88)	0.68(0.46,0.85)	0.64	0.85	0.81
No heavily	>0	49/119	100	170	223	57,81	49,90	57,80	0.74(0.58,0.86)	0.71(0.52,0.87)	0.66(0.49,0.81)	0.77	0.93	0.89
calcified	>1.25	40/110	101	170	223	62,82	52,90	67,80	0.76(0.50,0.88)	0.71(0.60,0.86)	0.72(0.54,0.86)	0.78	0.93	0.89
IPH areas	>2.80	25/95	104	162	223	68,84	68,87	80,80	0.83(0.71,0.91)	0.80(0.60,0.92)	0.80(0.66,0.91)	0.79	0.94	0.90

* IPH cutoff area=π $(0.63x)^2$, where 0.63mm was the in-plane the resolution of MP-RAGE, and x was set as 1 and 1.5 which gave areas of 1.25 and 2.80

**n+: number of slices with IPH present in histology, n:total number of slices

***Thresholds were optimized by maximizing the Youden's Index (sensitivity+specificity-1)

Discussion and Conclusion: Using histology as the gold standard, this study provides optimized thresholds for carotid IPH detection in MP-RAGE MRI using three different references. Of note, we found that the optimized threshold for the commonly used SCM reference method is 100%, suggesting that using of sternocleidomastoid muscle as reference may be problematic without intensity correction for the surface coil. Also of note, while overall detection and quantification performance was higher for larger areas of IPH and those without co-localized calcification, the optimal threshold was found to be stable regardless of the present/absence of these characteristics. Furthermore, a threshold of 162% based on AST has good IPH detection performance with high area correlation coefficient r=0.84-0.94 and thus is recommended for IPH detection where adjacent, isointense soft tissue region can be manually defined by reviews. For a fully automated IPH detection, the local median is the optimal choice for efficiency and accuracy, considering that the threshold of 223% based on MED is almost as accurate as AST with r=0.81-0.90. Figure 2 provides thresholds for selecting the desired optimum sensitivity, specificity and IPH area ratio (e.g. a threshold with higher sensitivity may be preferred to screen patients for IPH). In conclusion, this study provides optimized thresholds for carotid IPH identification in MP-RAGE images, with which automatically classified IPH areas were shown to highly correlate with those in histology.

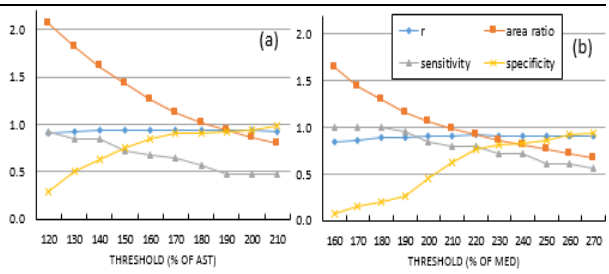

Figure 2 Statistical parameter curves using different thresholds based on two types of references **(a)** AST (adjacent soft tissue) **(b)** MED (median value within ROI). r: Pearson's correlation coefficient between IPH areas detected in MP-RAGE images using specific threshold and those in histology; area ratio: ratio of IPH areas measured in MP-RAGE images over those in histology; sensitivity and specificity are based on whether IPH is present or absent in each slice. (Heavily calcified IPH areas and IPH area<2.80mm^2 excluded, n=95)

Reference: 1. Kolodgie, F.D., et al., 2003. **349**: 2316-25. 2. Chu, B., et al., Stroke, 2004. **35**: 1079-84. 3. Ota, H., et al., 2010. **254**: 551-63. 4. Altaf, N., et al., J Vasc Surg, 2008. **47**: 337-42. 5. Hishikawa, T., et al., *Clinical article.* J Neurosurg, 2010. **113**: 890-6. 6. Zhu, D.C., et al., Magn Reson Imaging, 2008. **26**: 1360-6.