Intraplaque Hemorrhage Detection and Threshold Selection for Simultaneous Noncontrast Angiography and IntraPlaque Hemorrhage (SNAP) Images

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Introduction: Intraplaque hemorrhage (IPH) plays an important role in atherosclerosis progression and destabilization [1]. The SNAP sequence has been developed to detect IPH [2]: in theory, it offers the highest sensitivity to IPH among existing techniques as it takes the advantage of an improved dynamic range offered by phase-sensitive reconstruction. Although SNAP's performance in detecting hemorrhage has been compared with existing techniques, full validation with histology is needed before full clinical adoption. In addition, an optimized IPH detection criteria was needed for (semi)automatic image review. **Aims:** 1) To optimize SNAP detection criteria for IPH detection using histology as the gold standard; 2) to evaluate the sensitivity and specificity of SNAP in detecting hemorrhage.

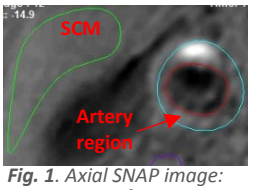

Fig. 1*. Axial SNAP image: artery region for IPH detection and reference sternocledomastoid (SCM)*

Materials and Methods: Subjects: 14 patients scheduled for carotid endarterectomy (CEA) were recruited and consented. MRI: All patients were scanned with 3T MRI (Philips R3.2.1, Best, the Netherlands) before surgery. The sequences included 3D SNAP (TR/TE/TI = 10/4.7/500 ms, resolution = 0.80×0.80×0.80 mm^3), Magnetization-Prepared Rapid Acquisition Gradient-Echo (MP-RAGE, TR/TE/TI = 13.2/4.6/304 ms, resolution = 0.63×0.63×2 mm^3), TOF, PD, T1W and T2W [3]. The thickness of axial slices of PD, T1W, T2W, MP-RAGE were 2mm. Histology: Following CEA, carotid plaque specimens were formalin fixed, decalcified, embedded in paraffin, and sectioned at 0.5 mm (above bifurcation) and 1mm (below bifurcation). An experienced histologist, blinded to SNAP and MPRAGE results, recorded presence/ absence and area of IPH for each section, and matched sections to standard multi-contrast images. MRI data analysis: SNAP images were reformatted to 2mm thick slices to match the 2D protocol. Lumen and outer wall contours were drawn to delineate the artery region (**Fig. 1**) for IPH detection. Three methods were utilized for threshold optimization: 1) original pixel intensity divided by mean sternocleidomastoid (SCM) intensity in the same slice (**Fig. 1**); 2) original pixel intensity divided by median value (MED) of all pixels with positive intensity in the same slice; and 3) used the original SNAP image pixel intensity without reference (NoRef). The original pixel value without reference were chosen because SNAP images were pre-adjusted for surface coil sensitivity during acquisition. Data analysis: receiver operator characteristic (ROC) curves and the area under the curve (AUC) were calculated by comparing the presence/ absence of IPH in MR images with that in matched histology slices. The threshold to detect IPH was optimized by maximizing Youden's Index (sensitivity + specificity -1). In order to eliminate the effect of co-localized calcification and resolution limits of MRI, sub-sets of data excluding slices with small IPH areas or calcified IPH calcified were also analyzed. AUCs for detecting presence/absence of hemorrhage in MP-RAGE images using various thresholds were also calculated, referring to the method in [4]. Comparisons of hemorrhage detection AUC between SNAP and MP-RAGE were performed using the non-parametric bootstrap.

Table 1*. Optimized thresholds and their performance in detecting hemorrhage with SNAP*

Data subset			AUC			Optimized threshold			Sensitivity,Specificity (%)		
	$\pi(x \cdot \text{pixel length})^2$*	n+/n**	SCM	MED	NoRef	SCM	MED	NoRef	SCM	MED	NoRef
With CA	**0**	**49/121**	0.74	0.77	**0.81**	4.23	5.36	**715**	47,94	55,93	**57,97**
	1	40/112	0.76	0.80	0.85	4.23	5.39	715	58,94	68,93	68,97
	1.5	30/102	0.80	0.84	0.89	4.23	6.63	740	60,94	67,99	73,97
No CA***	0	40/109	0.77	0.80	0.83	4.23	5.39	624	50,94	60,93	73,88
	1	33/102	0.81	0.84	0.87	4.23	5.39	715	61,94	73,93	73,97
	1.5	**23/92**	0.87	0.91	**0.93**	3.50	6.63	**740**	83,78	74,99	**83,97**

* $\pi(x \cdot \text{pixel length})^2$: excluding IPH with areas smaller than $\pi(x \cdot \text{pixel size})^2$, being 0, 2.01 and 4.52 mm^2 with x = 0, 1 and 1.5, respectively. Pixel length of SNAP was 0.8 mm.

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

***No CA: excluding calcified IPH.

Results: 121 MR slices with matched histology IPH information from 14 patients were analyzed (***Table 1***). AUC, sensitivity and specificity increased after excluding calcified IPH or smaller areas of IPH. By excluding small IPH of 1.5 times pixel length (4.52 mm^2) and calcified IPH, the optimized thresholds were 3.50 times the SCM, 6.63 times MED or 740 without reference. Among the three threshold methods, the original value (NoRef) had the best AUC (0.93) and sum of sensitivity and specificity (83% and 97%) (**Fig. 2**). The sensitivity and specificity of different thresholds are shown in **Fig. 3**. In the same sub-set data, using adjacent soft tissue and local median value as reference respectively, MPRAGE had an AUC of 0.86 and 0.87, sensitivity of 80% and 77%, and specificity of 87% and 91%. There was no statistical differences in the AUC for detecting IPH between SNAP and MP-RAGE (p>0.05).

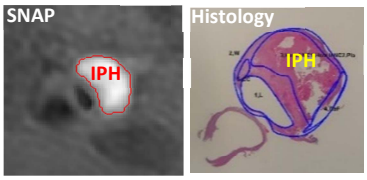

Fig. 2*. SNAP image and histology at the same location. IPH was detected by SNAP using a threshold of 740, which matched well with outlined IPH in histology*

Discussion: Results of this study indicate that a threshold using the original signal SNAP intensity without reference accurately identifies IPH *without* the need to measure signal in a reference region such as the adjacent SCM or surrounding tissue. Although SNAP had a higher AUC than MP-RAGE, they were not significantly different, which may due to the small sample size. However, SNAP has the advantages such as 1) higher contrast between IPH and surrounding tissue when compared with MP-RAGE [4] and, 2) IPH threshold can be easily based solely on original intensity value without reference. SNAP IPH detection sensitivity may be reduced due to: image resolution, co-localization of calcification with IPH, imperfect matching between histology and MR images, poor image quality with motion artifact, and the physiological state of IPH which may determine hyper intensity. An absolute intensity of 740 was found to provide the best total sensitivity and specificity, but Figure 3 can be used to choose a different threshold where higher sensitivity or specificity is required (**Fig. 3**). For example, when screening patients for IPH a lower threshold value can be used to obtain a higher sensitivity for IPH.

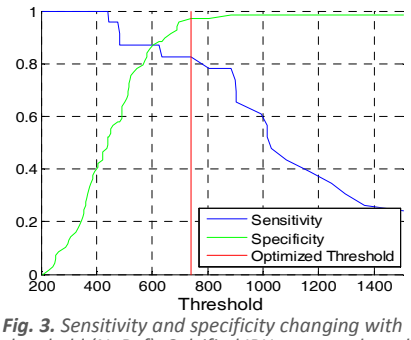

Fig. 3*. Sensitivity and specificity changing with threshold (NoRef). Calcified IPH areas and small IPH areas < 4.52 mm^2 were excluded.*

Conclusion: Using histological gold standard, findings from this study demonstrate that MR imaging with SNAP accurately identifies carotid intraplaque hemorrhage in vivo. In addition, a threshold of 740 based on the original intensity of SNAP images allowed carotid IPH to be detected automatically.

Reference: [1] Kolodgie F.D., et al., 2003, N Engl J Med, 349(24): 2316-25. [2] Wang J., et al., 2013, MRM, 69(2):337-45. [3] Yuan C., et al., 2001, Circulation, 104(17):2051-6. [4] Liu J., et al., 2014, ISMRM.