In vivo quantification of lipid-rich necrotic core using contrast-enhanced three-dimensional vessel wall imaging

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Introduction: The accumulation of lipids, cell debris, and importantly, intraplaque hemorrhages (IPH), leads to the formation and enlargement of lipid-rich necrotic core (LRNC) – a hallmark feature of vulnerable atherosclerotic plaques.[1] MRI has emerged as a viable tool for noninvasively measuring LRNC size. This is typically achieved by using multi-contrast MRI where multiple sequences offer complementary and corroborating contrast information that is essential for classifying LRNC areas in advanced plaques where other components are also commonly present.[2,3,4] A number of 3D sequences with improved time efficiency and isotropic spatial resolution have been developed. Yet no attempt has been made to combine them for in vivo assessment of LRNC. Furthermore, despite the well demonstrated advantage of using contrast for LRNC quantification in 2D MRI studies,[3,4] no previous studies have utilized contrast-enhanced 3D imaging. **Purpose:** We hypothesized that a parsimonious combination of 3D sequences, selected based on their contrast characteristics, would allow accurate identification and quantification of LRNC in a time-efficient manner. **Methods:** *Study sample:* Eight patients with mild to severe carotid stenosis were recruited. Bilateral carotids were included to further ensure a broad range of lesion severity. *3D multi-contrast MRI:* A 3D motion-sensitized driven equilibrium prepared rapid gradient echo sequence (3D-MERGE),[5] and the simultaneous noncontrast angiography and intraplaque hemorrhage sequence (SNAP)[6] were used to build a 3D multi-contrast protocol with isotropic resolution (0.8X0.8X0.8 mm^3), large coverage (16 cm), and reduced scan time (<20 minutes including contrast injection). 3D-MERGE was scanned twice, before and after gadolinium contrast injection. *2D multi-contrast MRI:* A histologically validated 2D multi-contrast MRI protocol[3,7] was used as reference: spatial resolution = 0.63X0.63X2 mm^3, coverage = 3.2 cm, total scan time>35 minutes. The T1-weighted sequence was scanned twice, before and after gadolinium contrast injection. *MRI scan:* Subjects were scanned using a 3T scanner (Philips Achieva, R3.21, the Netherlands) and a custom eight-channel phased-array surface coil. 2D and 3D protocols were performed in the same session. The T1-weighted TSE sequence and 3D-MERGE were repeated 5-10 minutes after contrast injection to get contrast-enhanced images. *Image analysis:* To facilitate matching and comparison, 3D image volumes were reformatted into 2 mm axial slices. The two axial image sets (2D and 3D) were then aligned using the carotid bifurcation as a landmark, which would automatically match all slices based on distance to bifurcation. Last, matched 2D and 3D images were reviewed independently by experienced readers for LRNC, calcification and IPH. We used established tissue classification criteria in 2D review, and set new criteria in 3D review based on contrast characteristics of each sequence (Table 1). *Statistical analysis:* Cohen's kappa and intra-class correlation coefficient (ICC) with 95% confidence intervals (CI) were used.

Table 1: Tissue classification criteria for 3D multi-contrast review.

	pre-contrast 3D-MERGE	post-contrast 3D-MERGE	SNAP
Fibrous tissue	0 / +	0 / +	0
Calcification	- - -	- - -	0 / -
LRNC			
without IPH	0 / -	- -	0
with IPH	+	-	+ + +

Signal intensities are relative to adjacent muscle or fibrous tissue.
+: hyperintense; 0: isointense; -: hypointense.

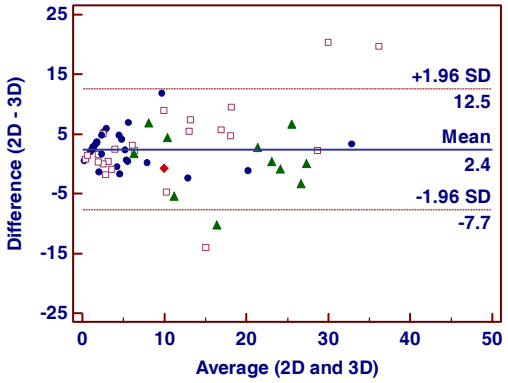

Table 2: Agreement between 2D and 3D protocols in LRNC area measurement.

	ICC	95% CI
Overall (n=65)	0.84	0.70 - 0.91
Presence/absence of other components		
no other components (n=29)	0.86	0.45 – 0.95
with accompanying calcification (n=35)	0.79	0.62 – 0.89
with IPH (n=12)	0.84	0.52 – 0.95

Figure 1 (left): Bland-Altman plot of LRNC area measurement. Data points were plotted as subgroups according to presence/absence of other components: no other components (solid circle), calcification only (hollow square), IPH only (solid rhombus), calcification and IPH (solid triangle).

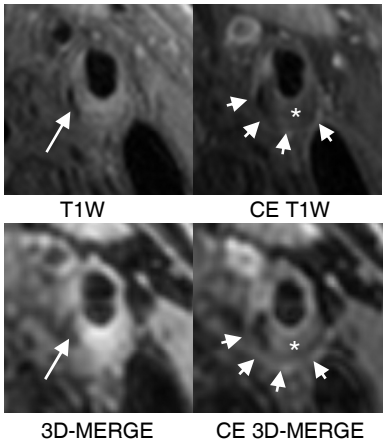

Figure 2: Matched 2D and 3D images delineate LRNC in a similar way. LRNC (asterisk) and calcification (long arrow) appear distinct in both 2D (upper panel) and 3D (lower panel) images. Short arrows indicate outer wall boundaries.

Results: A total of 239 matched slices were available for comparison. 2D multicontrast images indicated LRNC in 65 (27.2%) slices, of which 35 were accompanied by calcification, 12 with IPH, and 29 without IPH or accompanying calcification (Table 2). *LRNC identification:* 2D and 3D image reviews agreed on LRNC identification in 87% of slices, yielding a kappa value of 0.66 (95% CI: 0.56, 0.77). *LRNC quantification:* An overall good agreement was observed between 2D and 3D images in measuring LRNC size (ICC: 0.84; 95% CI: 0.70, 0.91) in the subset of slices with LRNC shown by 2D images (Figure 2). Moreover, the good agreement was consistent regardless of whether there are other components such as calcification and IPH (Table 2). **Discussion:** Our aim was to test if combing SNAP and pre- and post-contrast 3D-MERGE would provide sufficient contrast information to allow LRNC identification and quantification across various lesion complexities. Thus, to achieve slice-level agreement is both critical and informative. Despite possible mismatching and/or different slice obliquity that are inevitable in comparing slice-based measurements, our preliminary data suggested a good agreement between 2D and 3D multi-contrast protocols in LRNC delineation, which did not appear to be influenced by lesion complexities. With scan time reduced by half and coverage increased by 5-fold compared to the traditional 2D protocol, the 3D multi-contrast protocol may prove invaluable in future clinical studies of LRNC. **Conclusion:** In vivo quantification of LRNC is feasible using 3D MRI with contrast-enhanced imaging. Our data add supporting evidence to the pursuit of a fully 3D imaging approach for characterizing plaque tissue composition.

References: 1. Narula J, et al. *JACC,* 2013; 2. Trivedi RA, et al. *Neuroradiology*, 2004; 3. Cai J, et al. *Circulation*, 2005; 4. Wasserman BA, et al. *Stroke*, 2008; 5. Balu N, et al. *MRM*, 2011; 6. Wang J, et al. *MRM*, 2013; 7. Li F, et al. *JMRI*, 2009.