Published in final edited form as:

J Neurointerv Surg. 2018 February ; 10(2): 143–149. doi:10.1136/neurintsurg-2016-012974.

Development of a High-resolution MRI (HRMRI) Intracranial Atherosclerosis Imaging Phantom

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Abstract

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Contributorship Statement:

JYC, KVDM, MJG, TL, TRB, SA, TJC, ARC, RHS, EF and TNT: designed the phantom and imaging experiments, performed the experiments, analyzed and processed the data, drafted the manuscript. RMK and OWB: contributed to phantom modeling and MR characterization, revised the draft manuscript. TL, TRB, SA, TJC, AKB, XJZ, HM, SZ, JWR, and RHS: acquired imaging data, revised the manuscript.

Data Sharing:

For access to the raw images obtained in this study, please contact the corresponding author.

Competing Interests Statement:

MJG: Has been a consultant on a fee-per-hour basis for Codman Neurovascular, InNeuroCo Inc, and Stryker Neurovascular; holds stock in InNeuroCo; and research support from the National Institutes of Health (NIH), Cerevasc LLC, Codman Neurovascular, the Cure Tay Sachs Foundation, and Genuity LLC, InNeuroCo, Medtronic Neurovascular, Microvention/Terumo, Mivi Neuroscience, Neuravi, Neurogami, Neuronal Protection Systems, Rapid Medical, R92M LLC, Philips Healthcare, Stryker Neurovascular, the Wyss Institute.

SA: NIH 1R21HL130969

RHS: The Heart and Stroke Foundation of Canada New Investigator Award, the Canadian Partnership for Stroke Recovery and the Department of Medicine at Sunnybrook and University of Toronto.

TNT: NINDS 5R21-TW010356-02

BACKGROUND AND PURPOSE—Currently, there is neither a standard protocol for vessel wall MR-imaging of intracranial atherosclerotic disease (ICAD), nor a gold standard phantom to compare MR-sequences. In this study, a plaque phantom is developed and characterized that provides a platform for establishing a uniform imaging approach for ICAD.

MATERIALS AND METHODS—A patient-specific injection mold was 3D-printed to construct a geometrically accurate ICAD phantom. Polyvinyl alcohol hydrogel was infused into the core-shell mold to form the stenotic artery. The ICAD phantom incorporated materials mimicking a stenotic vessel and plaque components including fibrous cap and lipid core. Two phantoms were scanned using high-resolution cone-beam CT and compared to four different 3T MRI systems across 8 different sites over the period of 18 months. Inter-phantom variability was assessed by lumen dimensions and contrast-to-noise ratio (CNR).

RESULTS—Quantitative evaluation of the minimum lumen radius in the stenosis showed that the radius was on average 0.80mm (95% CI: [0.77, 0.82]mm) in model 1 and 0.77mm (95% CI: [0.74, 0.81]mm) in model 2. The highest CNRs were observed for comparisons between lipid and vessel wall. To evaluate the manufacturing reproducibility, the CNR variability between the two models had an average absolute difference of 4.31 (95% CI: [3.82, 5.78]). Variation in CNR between the images from the same scanner separated by 7 months was 2.5–6.2, showing reproducible phantom durability.

CONCLUSIONS—A plaque phantom composed of a stenotic vessel wall and plaque components was successfully constructed for multi-center high-resolution MRI standardization.

Keywords

Atherosclerosis; MRI; Stenosis; Vessel Wall

Introduction

Recent randomized trials showed that despite treatment of intracranial atherosclerosis (ICAD) with aggressive medical management, some patients still have a high risk of stroke.^{1, 2} More rigorous patient selection based on characteristics of intracranial plaques may make it possible to identify patients who would benefit from new therapies, such as refined endovascular procedures^{3–5} or novel medical therapies. High resolution MRI (HRMRI) is also a promising technique to differentiate various pathologies that may be the cause of intracranial artery stenosis (e.g. atherosclerosis vs. vasculitis vs. other vasculopathy) and allow characterization of ICAD plaque composition.^{6–10} While HRMRI research has been growing throughout the past decade with great success in carotid artery plaque analysis,^{11, 12} its clinical application to ICAD has been limited by a lack of standardization. The approach to developing HRMRI imaging in ICAD has been fragmented, with most investigators focused on designing and validating their own sequences in small, underpowered, single-center studies. There is currently no universal standard protocol for HRMRI imaging that would facilitate multicenter studies. Furthermore, data generated by HRMRI is dependent on MR instrumentation, sequence parameters used, the MR environment, and well as patient factors, which can make comparisons of results from multiple centers difficult. In order to advance the field of HRMRI ICAD research, establishment of a multicenter network to

provide a research infrastructure for promoting collaboration, sharing of protocols and data, and providing a quick and efficient mechanism for studying HRMRI in ICAD is needed. A critical factor for the development of such a multicenter HRMRI ICAD network, is the need for a static model, or phantom, to standardize image quality across sequences and centers.

We have developed a patient-specific basilar artery stenosis imaging phantom to provide the image quality assessment and standardization that is required for the development of a multi-center international HRMRI ICAD network. Our MRI phantom has been specially designed to evaluate, analyze, and optimize the performance of MRI scanners or sequences suitable for imaging small structures. Since the intracranial arteries are very small (average diameter 2–5 mm), with even smaller plaque components, the ability of an individual MRI scanner to generate high quality images of such small structures must be established. Our phantom is based on details from a patient's HRMRI ICAD images, and will enable practical assessment of the image quality obtained from HRMRI sequences using various MR instruments at various sites, without subjecting multiple human subjects to long time-periods in the MRI scanner and controlling for patient motion artifacts, during sequence assessment and optimization. Herein, we describe the design and construction of the phantom and the methods used to assess MR image quality at multiple sites.

Methods

Phantom construction

With permission of our Institutional Review Board and informed consent, HRMRI imaging data from a patient with intracranial atherosclerotic disease was used to acquire a detailed structure of plaque components (Figure 1A). The images were segmented for the lumen, fibrous cap and lipid core (Mimics and Magics; Materialise, Leuven, Belgium) (Figure 1B). The computer model (Figure 2A) was used to create the infusion mold by 3D printing (Figure 2B), as previously described.¹³ Polyvinyl alcohol (PVA Mowiol® 56–98, Höchst AG, Frankfurt/Main, Germany) with an average molecular weight of 195,000 g/mol and a hydrolysis degree of 98% was mixed with dimethyl sulfoxide (DMSO, D4540, Sigma-Aldrich, St. Louis, MO) and water. The mixture was allowed to cool to the room temperature and was then infused into the acrylonitrile butadiene styrene (ABS) core-shell mold by liquid injection molding, followed by 3 freeze-thaw cycles for curing. The core-shell mold was immersed in xylene for ABS dissolution, yielding a PVA stenotic vessel wall (Figure 2C).

The segmented fibrous cap was mimicked by a mixture of 0.41 wt.% gadolinium chloride, 0.44 wt.% agarose, 3 wt.% carrageenan, 0.05 wt.% sodium azide, 96 wt.% water, and 0.1 wt.% sodium chloride. A lipid core was simulated using a 95.95 wt.% milk, 0.05 wt.% sodium azide, and 4 wt.% carrageenan mixture. Milk was selected over other oil-based solutions since as an emulsion of fat and water with the major lipid component being triglycerides, dissolution and dispersion of the carrageenan (a high molecular weight polysaccharide) was more controllably achieved. To precisely control the volume of each plaque component, a plaque mold made of silicone with known shape and dimension was built. Each mixture was infused into the silicone container, and set at -80°C for 1 hour. The silicone container was carefully cut open to release the shaped plaque component. The shaped plaque components

were then glued to the PVA vascular replica of a stenotic vessel wall by adding several layers of PVA coating and performing curing process. Two samples of the phantom were manufactured and each secured in a closed 50 ml centrifuge tube. The models were secured by two through holes at either end of the centrifuge container secured by a friction fit with silicone tubes that attached to the model. The centrifuge container was filled with distilled water to maintain hydration of the PVA phantom.

Imaging of the phantom

The plaque phantom was scanned using four different 3T MRI platforms (Siemens Trio, Siemens Skyra, Philips Achieva, GE MR750 Discovery) at 8 different sites. The details of the MR scanner types and parameters are shown in Table 1. For each experiment, the two phantom models were imaged side-by-side using a 3D T2-weighted sequence and imaging planes were planned to provide cross-sectional thin-slice views centered on the stenosis of both phantoms. In addition, longitudinal slices through each phantom were acquired with a multi-slice T2-weighted sequence.

We also explored the utility of high-resolution cone-beam CT to provide a detailed benchmark of lumen geometry for HRMRI-based stenosis measurements. Three stenotic vessel wall models were constructed using the techniques described above, filled with Omnipaque 350, sealed with a 3-way stopcock, and embedded in water. Images were reconstructed at an isotropic resolution of 0.20 mm from VasoCT acquisitions¹⁴ obtained with a monoplanar angiographic system (Allura Xper FD20, Philips Healthcare).

Image quality assessment

Quantitative comparisons of the scan results for both structural dimensions of plaque components (e.g. lumen radius) and image contrast between plaque components were based on the thin cross-sectional slices from 3D T2-weighted TSE/FSE acquisitions. The two imaged phantoms in the field-of-view were extracted from the background and fluid-filled tube using manually initialized region growing segmentations and separately analyzed, as shown in Figure 3. Global affine and diffeomorphic non-rigid image registrations were performed to capture geometric variability using elastix¹⁵ and ANTs¹⁶. In an iterative fashion, all images were aligned with a template that was subsequently refined to represent the mean geometry and image intensity following a strategy employed in the construction of population-average brain models¹⁷. During each pair-wise registration step, a mutual information similarity metric was optimized. Average transformation matrices¹⁸ and deformation fields were used to define an updated template space, and a refined template in this space was obtained by weighted averaging of normalized image intensity values. Templates were refined using 10 iterative registration- and normalization steps. Projections of the regions of interest onto the original image slices were visually inspected to ensure adequate delineation of the vessel wall and plaque components in scans of both models.

Lumen diameter was determined on the final instance of the template and on images of each individual sample, as well as on the CT scans. The Vascular Modeling Toolkit (VMTK)¹⁹ was employed to extract and refine a surface representation of the lumen using a manually initialized level-set segmentation from each image. The radius of the maximum inscribed

sphere was calculated at each point along the central axis of the individual image's surface models, and all values were mapped to the corresponding position along the central axis of the template model using the spatial transformations that were previously calculated. Variation in measured lumen geometry was characterized by calculation of the weighted mean and standard deviation of the sample radii at every point along the template model's central axis. Due to the limited field-of-view in the slice direction and slight variations in sample positioning within the containers, cross-sections could be planned optimally only for one of the two samples imaged. Samples with partial slice coverage of the stenosis did not contribute to the template refinement procedure and were also excluded from mean lumen diameter measurements. To reduce the contribution of less reliable radius calculations based on boundary slices, weighting values tapered off with a smooth Gaussian profile near the sample's centerline endpoints.

Image contrast between constituent components of the plaque phantom, i.e. lipid core, fibrous cap, and vessel wall, was assessed by calculating a contrast-to-noise ratio (CNR) for each pair of components, which was defined as the quotient of the difference between the mean intensities and the standard deviation of the background noise. Intensity measurements were obtained in regions that were first defined semi-automatically on the final template image. These binary segmentations of the vessel wall, lipid core, and fibrous cap, were obtained from each template image by evolving active-contours as implemented in ITK-SNAP²⁰. Segmentations were then projected to original images using the transformations computed before in order to calculate intensity means and standard deviations. Regions for background signal extraction were manually defined in each image.

In order to evaluate reproducibility and accuracy of the phantom model construction, percent stenosis calculations were used to compare lumen diameter profiles extracted from the average HRMRI scans of the two phantoms with the average VMTK-based lumen diameter profile obtained from CT scans of the three stenotic vessel wall models. Additionally, the minimum lumen diameter of the stenotic segment was measured and the 95% confidence interval calculated. To evaluate temporal durability of the phantom, lumen diameter and image contrast were compared between phantom images acquired from the same Siemens Skyra scanner performed 7 months apart (scans # 1 and 5). To evaluate reproducibility of the phantom images between different MR platforms, image contrast and lumen diameter were compared between scanner models, software, and locations. Within-sample absolute differences in CNR between model 1 and model 2 were calculated to estimate image contrast variability between models. We subsequently determined the mean variability over all samples and contrast components, and a bootstrap estimate the 95% confidence interval of the mean.

Results

Cross-sectional HRMRI images of the two phantom models were acquired on 10 occasions at eight different sites (Figure 4). For each of the two phantom models, a template image in a reference coordinate system was constructed using 10 iterations of registration and averaging, and used to identify plaque components. Quantitative evaluation of the visible lumen diameter in the vicinity of the stenosis (Figure 5) shows that there is minimal

variation between the scans, demonstrating reproducibility between scanner types. In addition, the two phantom models yielded very similar radius profiles before and at the stenotic portion of the vessel axis (Figure 5A versus Figure 5B) demonstrating reproducibility in phantom manufacture. Unbinned contrast-enhanced cone-beam CT acquisitions of three stenotic vessel wall models without plaques were used to calculate reference percent stenosis values along the vessel axis (Figure 6). The minimum radius along the stenosis was on average 0.80 mm (95% confidence interval: [0.77, 0.82] mm) in model 1 and 0.77 mm (95% confidence interval: [0.74, 0.81] mm) in model 2. The minimum radius of the stenosis measured on the patient's HRMRI (0.75mm) was slightly smaller than the model, but the difference was within the resolution of the measurement.

CNR measurements were obtained for each scan based on the back-projected delineations of the vessel wall and the two plaque components (Table 2). Overall, the highest CNRs were observed for comparisons between lipid (hyperintense on T2-weighted images) and the vessel wall (hypointense). Intra-plaque CNRs ranged from 2.7 to 49.9 with a mean value of 19.4 and a median value of 16.3, and >4.5 in 85% of the samples. Image contrast variability between the two phantom models for each comparison between plaque components was 3.81–5.16, with overall absolute difference in CNR of 4.31 (95% confidence interval=[3.82, 5.78]). These small variations relative to consistently high plaque component CNR values confirm reliability in manufacturing technique. Variation in CNR between the two models imaged on the same scanner separated by 7 months (scans #1 and 5) was 2.15–6.16, showing again reproducible phantom characteristics over time. However, there was a large increase in CNR during this time period within each model (13.8±5.8).

Discussion

Intracranial atherosclerotic disease is the most common cause of stroke worldwide with a high risk of recurrent stroke; but despite the impact, little is known about how intracranial plaque characteristics are related to the risk of stroke. High-resolution vessel wall MRI is a promising tool for understanding the pathology, yet multicenter prospective studies are needed to determine the relationship between plaque components and stroke risk. A critical factor for the development of such a multicenter studies is the need for a static phantom to standardize HRMRI image quality between sequences and centers. In this report, we described our first effort to align HRMRI protocols and equipment among different sites for comprehensive assessment of ICAD plaques. Our HRMRI ICAD phantom, based on actual HRMRI images of a basilar stenosis, is a durable model that allows for highly reproducible images and is therefore a promising tool for quality control and sequence implementation at multiple sites. Our manufacturing technique results in phantoms with very similar imaging characteristics, allowing for multiple phantoms to be developed for reproducibility between sites. Combined with standardized image post-processing to quantify image quality, lumen geometry, and plaque characteristics, our reproducible phantom offers a platform for collaborative development and validation of dedicated ICAD imaging protocols. We did observe a stable drift in contrast of the phantom plaque components over time that although reproducible suggest further improvements in phantom stability are desired or the inclusion of a contrast standard for normalization should be used.

Desired characteristics of an ICAD phantom include: 1) reproducibility and structural stability; 2) physiologically relevant size and geometry; and 3) distinguishable HRMRI characteristics between plaque components. In this work, 3D printing provides geometrically accurate ICAD phantoms based on patient data for HRMRI imaging.

The challenges of developing a HRMRI phantom include selection of materials that can provide luminal detail and allow for insertion of additional plaque components. PVA is a polymer that has been extensively studied due to its numerous desirable characteristics such as biocompatibility and aggregating gel formation. These properties make PVA a good material for various biomedical applications, such as an MR imaging phantom. PVA hydrogel was adopted to mimic the vessel wall in this study because it is elastic and has high water content, enabling the creation of phantoms in a range of different shapes. Unlike silicone vascular replicas that have no MR signal, PVA traps water and its composition easily altered to adjust MR imaging characteristics. PVA hydrogel is a well-known crystallization-induced physical gel, and is composed of crystalline regions (junction zones) and amorphous regions (long flexible chains). Crystallites act as junction points, and the crystallinity determines the physical properties of the PVA hydrogel. During the freeze/thaw process, freezing causes phase separation, which is followed by crystallization of the PVA chains. Phase separation is retarded by addition of DMSO. Under such condition, post-gelatin crystallization is allowed to proceed and a homogeneous gel structure is formed. As a result, the mechanical properties of the PVA hydrogel are improved. The improvement in mechanical properties of the PVA hydrogel prevents the PVA vessel wall from collapsing during HRMRI imaging. An additional benefit of using an appropriate ratio of PVA and DMSO is that a gel can be formed with MR relaxation times comparable to those of human tissue.

Our work has limitations, which include the lack of all ICAD plaque components in the phantom, specifically intra-plaque hemorrhage and calcification that are seen in atherosclerotic disease. However, in future generations of ICAD phantoms, these components can be included in the model. Another limitation is that the phantom was scanned in an artificially static environment without intraluminal flow. Circulation of a blood analog and an MR compatible cardiac pulse duplicator could be incorporated into future models to generate realistic flow waveforms to account for the impact of flow on HRMRI ICAD imaging. However, this additional complexity may limit adoption of the phantom in application. Also, we limited the imaging evaluation of the phantom plaque components to T2-weighted MRI. Pre- and post-contrast T1 images should be assessed in future analyses of phantom model performance. In future studies, our analysis methodology with intensity- and geometry-based measurements obtained from additional MRI sequences after image co-registration could be applied. Finally, we did not capture data on the true value of the phantom; specifically, the hours spent imaging the phantom and adjusting MR technique to generate acceptable images for analysis. In certain centers, the phantom was used to optimize image acquisition in advance of implementing HRMRI in clinical studies. These metrics would have demonstrated the clear, pragmatic advantages of such a phantom.

We have described a strategy to develop a segmented template image in an unbiased reference coordinate system to quantitatively compare geometric properties and image

intensity characteristics among model images acquired at different sites and scanners. Our registration approach followed techniques established in computational anatomy to obtain unbiased templates representing average anatomical shape and acquisition-dependent intensity variation^{17, 21}. Image quality assessment was achieved using public domain implementations of established image analysis algorithms and required little user interaction. HRMRI lumen diameters could be compared against the values obtained with detailed cone-beam CT imaging. Within this framework CNR measurements can be used to define lower bounds on acceptable image quality.

Conclusions

A technique has been described to manufacture realistic ICAD phantoms. The resulting phantom is reproducible and structurally stable, which enables efficient assessment of the image quality obtained from HRMRI sequences using various MRI manufacturers at various sites.

Acknowledgments

Funding Statement:

This work was supported in part by NINDS 5R21-TW010356-02 (to TNT). The content is solely the responsibility of the authors, and does not represent the official views of the NIH.

Abbreviations

HRMRI	high resolution MRI
ICAD	intracranial atherosclerotic disease
STL	stereolithography
PVA	polyvinyl alcohol
DMSO	dimethyl sulfoxide
ABS	acrylonitrile butadiene styrene
VMTK	vascular modeling toolkit
CNR	contrast-to-noise ratio

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Figure 1.

Frontal maximum intensity projection image from time-of-flight MR showing a focal stenosis of the basilar artery (A, top panel, arrow). Single axial slice of high-resolution vessel wall MRI showing intracranial atherosclerosis of the basilar artery (A, bottom panel, arrow). The resulting patient-specific virtual phantom of atherosclerotic plaque (B) with fibrous cap (C, top panel) and lipid core (C, bottom panel).

Figure 2.

(A) The stenotic basilar artery is used as a “core” to build a core-shell mold (B). Hydrogel is infused into the core-shell model and undergoes several freeze-thaw cycles for curing. After mold dissolution in xylene, a hydrogel vascular replica is obtained (C).

Figure 3.

Each row represents a set of 3D T2-weighted TSE slices for sample model #1 and #2 scanned at one of the participating sites. After spatial normalization and intensity normalization, semi-automatic segmentation was performed to define the vessel wall (blue), lumen (yellow), lipid core (green), and fibrous cap (red). These segmentations were projected onto a selection of original image slices as displayed above.

Figure 4. Cross-sectional T2 HRMRI images of the two phantom models acquired on 10 occasions at eight different sites (see Table 1 for site location and scan details).

Figure 5.

Weighted mean and 95% confidence interval of selected samples' maximum inscribed sphere radii along the centerline (abscissa) of the template model for phantom model #1 (A) and model #2 (B) as measured by Vascular Modeling Toolkit. Maximum inscribed sphere radii plotted for each individual sample in phantom model #1 (C) and model #2 (D) as measured by HRMRI. Only samples with slices covering the stenosis were included (black striped line indicates extent of abscissa overlap among all selected samples).

Figure 6.

Percent stenosis measurements were obtained from average lumen radius computations on high-resolution cone-beam CT scans of three stenotic vessel wall models (red line) and compared to similar measurements on average HRMRI scans of phantom model 1 (blue) and 2 (green). The radius at 5 mm before the maximum stenosis was used as reference for conversion of radii to percent stenosis values.

Table 1

MRI models and parameters for phantom scan comparisons

sample no.	location	scanner	model	scan date	slice thickness	slice number	resolution	FOV	TR	TE
1	MUSC	Siemens	Trio	10/7/2014	1.2mm	32	0.25×0.25	64×64	1500	66
2	Emory	Siemens	Skyra	11/18/2014	1.2mm	18	0.25×0.25	64×64	1500	66
3	UMass	Philips	Achieva	2/24/2015	1.2mm	18	0.361×0.361	260×240	1500	66
4	MUSC	Siemens	Trio	4/24/2015	1.2mm	18	0.25×0.25	104×104	1500	66
5	MUSC	Siemens	Trio	5/11/2015	1.2mm	18	0.25×0.25	64×64	1500	66
6	PUMC	Siemens	Skyra	6/8/2015	1.2mm	18	0.234×0.234	64×64	1500	69
7	UC	Philips	Achieva	8/21/2015	1.2mm	18	0.36×0.36	64×64	1500	66
8	NW	Siemens	Skyra	9/14/2015	1.2mm	18	0.234×0.234	58×60	1500	69
9	Vanderbilt	Philips	Achieva	1/14/2016	1.2mm	18	0.25×0.25	160×150	1500	66
10	ZJU	GE MR750	Discovery	4/8/2016	0.5mm	96	0.195×0.195	512×512	1500	113

MUSC – Medical University of South Carolina; UMass – University of Massachusetts Worcester; PUMC – Peking Union Medical College; UC – University of Chicago; NW – Northwestern University; ZJU - Zhejiang University

Table 2

Contrast-to-noise measurements for individual scans.

	Sample	Lipid core versus fibrous cap	Fibrous cap versus vessel wall	Lipid core versus vessel wall
Model #1	1	9.2	13.5	22.6
	2	11.6	16.6	28.1
	3	31.1	29.4	60.5
	4	49.9	41.3	91.2
	5	20.8	19.2	40.0
	6	16.3	13.6	29.9
	7	41.3	35.6	76.9
	8	16.2	15.5	31.7
	9	19.0	15.6	34.6
	10	3.4	2.4	5.8
Model #2	1	2.7	11.8	14.5
	2	4.5	15.8	20.3
	3	24.5	34.4	58.9
	4	33.1	56.2	89.3
	5	15.0	21.8	36.8
	6	11.8	16.2	28.0
	7	39.4	32.8	72.2
	8	14.6	18.2	32.8
	9	19.7	21.4	41.1
	10	3.7	3.2	6.9
Mean variability overall		10.48	9.94	20.24
Mean variability between Models 1 and 2		5.16	3.96	3.81
Mean variability between Scans 1 and 5		6.16	2.15	5.70
Mean variability between Siemens scanners *		5.09	2.07	4.46

* limited to Siemens scanners with similar FOV (scans 1, 2, 5, 6, 8)