

Received:
17 June 2020Revised:
14 October 2020Accepted:
09 November 2020<https://doi.org/10.1259/bjr.20200743>

Cite this article as:

Sarikaya B, Colip C, Hwang WD, Hippe DS, Zhu C, Sun J, et al. Comparison of time-of-flight MR angiography and intracranial vessel wall MRI for luminal measurements relative to CT angiography. *Br J Radiol* 2020; **94**: 20200743.

FULL PAPER

Comparison of time-of-flight MR angiography and intracranial vessel wall MRI for luminal measurements relative to CT angiography

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Objective: To assess whether intracranial vessel wall (IVW) MRI luminal measurements are more accurate than non-contrast 3D-TOF-MRA measurements for intracranial atherosclerotic stenosis, relative to CTA.

Methods: Consecutive patients with non-calcified intracranial atherosclerotic stenosis seen on CTA, who had non-contrast 3D-TOF-MRA and IVW performed between 1 January 2013 and 20 April 2014 were selected, and images with stenosis were pre-selected by a single independent rater. The pre-selected CTA, MRA, and IVW (T_1 -weighted) images were then reviewed by two independent raters blinded to the other measurements in random order. Measurements were made in a plane perpendicular to the lumen on each modality. MRA and IVW measurements were compared to CTA, to determine which more accurately matched the degree of stenosis.

Results: 18 patients with 33 intracranial atherosclerotic stenoses were included. Relative to CTA, IVW had 40% less variance than MRA ($p = .004$). IVW had a significantly higher concordance correlation coefficient (CCC) relative to CTA than MRA (.87 vs .68, $p = .002$). IVW and MRA did not have significant bias relative to CTA, however, 8/33 lesions showed >20% overestimation of the degree of stenosis on MRA, compared to 1/33 for IVW. CCC between raters were 0.84 (95% CI 0.67–0.93) for CTA, 0.83 (0.67–0.93) for TOF-MRA, and 0.85 (0.71–0.94) for IVW. For stenosis >50% sensitivity was 82% for IVW and 64% for MRA, while specificity was 73% for both.

Conclusion: IVW provides more accurate stenosis measurements than MRA when compared to CTA.

Advances in knowledge: Considering higher stenosis measurement accuracy of IVW, it can be more reliably used for quantitative evaluation relative to MRA.

INTRODUCTION

Currently, the evaluation of intracranial atherosclerotic arterial stenosis relies on luminal measurements using luminal imaging techniques, including digital subtraction catheter angiography (DSA), CT angiography (CTA), and MR angiography (MRA). While DSA is the gold standard in assessing luminal stenosis, most angiographic runs are performed as a 2D imaging acquisition and accurate assessment of stenosis may be difficult due to overlapping structures.^{1,2} In addition, DSA is an invasive technique with a small risk of stroke. Patients frequently undergo both CTA and MRI/MRA, and at some institutions, high-resolution vessel wall (IVW) imaging. While CTA provides good spatial resolution and assessment of luminal stenosis, this technique also exposes the patient to radiation as well as iodinated contrast, which has a risk of contrast-induced nephropathy and allergic reactions. Non-contrast time-of-flight MRA is the most frequently utilized

MR angiographic technique and provides good contrast resolution for luminal evaluation. In the setting of slow flow or high-grade stenosis, however, the degree of stenosis will frequently be overestimated due to flow dephasing artifacts and mild stenosis may also be underestimated due to bleeding effects of the vascular lumen.^{3,4} IVW is an increasingly utilized and reliable technique that allows for assessment of vessel wall pathology,^{5,6} including atherosclerosis,^{7,8} and has shown value in disease characterization^{9–11} and differentiation.^{12,13} We hypothesize that luminal measurements on IVW are more accurate than those on 3D-TOF-MRA, relative to CTA.

METHODS AND MATERIALS

Patient population

After institutional review board approval, the radiology database was retrospectively queried for patients with

intracranial arterial stenosis on CTA between the dates of 1 January 2013 and 20 April 2014. Inclusion criteria were: (1) CTA, TOF-MRA and pre- and post-contrast T1 IVW performed within 2 weeks of one another and available for review; (2) non-calcified intracranial arterial stenosis on CTA head; and (3) ≥ 2 vascular risk factors. Exclusion criteria were: (1) Lack of coverage of the target lesions on any of the imaging comparisons; (2) Lack of IVW acquisition in a plane perpendicular to the target lumen; (3) lack of post-contrast IVW sequences; and (4) any clinical or imaging evidence of other non-atherosclerotic vascular diseases (vasculitis, dissection, moyamoya disease, vasospasm, or reversible cerebral vasoconstriction syndrome).

Data abstraction

Electronic medical records were reviewed for patient data, specifically patient age, ethnicity, gender, vascular risk factors (dyslipidemia, hypertension, smoking, diabetes mellitus, age >50 for males and >55 for females, and obesity), and stroke history.

CTA protocol

CTA head/neck scanning protocol for stroke evaluation was performed on the 128-channel Siemens Somatom AS + scanner (Siemens Healthineers; Erlangen, Germany). 100 ml Omnipaque 350 i.v. contrast is injected at 5 ml/s followed by 30 ml normal saline flush injected at 5 ml/s via 18-gauge cannula placed in the antecubital vein. After contrast injection, SmartPrep was used for bolus timing with monitoring at the aortic arch with a 7 s scanning delay. Scanning is performed from the aortic arch through the vertex. Scanning parameters are: 250 mAs, 120 kVp, 0.9 pitch, 0.5 rotation, 128 \times 0.6 mm acquisition with 1 mm reconstructed slice thickness. Multiplanar reconstructions were performed with 1.0 mm thick slices.

Intracranial vessel wall imaging protocol

MRI was performed on a 3T Siemens Trio MRI system (Siemens Healthineers; Erlangen, Germany) with standard head coil. IVW MRI protocol consisted of 3D TOF-MRA, 2D T_2 -weighted, 2D T_1 -weighted pre- and post-contrast IVW performed in multiple planes, including axial planes and planes perpendicular to the course of the target lumen. For this study, the TOF-MRA and T_1 -weighted IVW pre- and post-contrast sequences were used. TOF-MRA parameters are: in-plane resolution, 0.53 \times 0.47 mm; slice thickness, 0.53 mm; repetition time/echo time, 20/3.69 ms; flip angle, 18; field of view, 205 \times 184 mm; time, 5:40 min. T_1 -weighted IVW parameters are: in-plane resolution, 0.4 \times 0.35 mm; slice thickness, 2 mm; repetition time/echo time, 1000/10 ms; averages, 4; matrix, 448 \times 448 pixels; field of view, 180 \times 158 mm; GRAPPA factor, 2; turbo factor, 18; time, 36 s per slice.

Data analysis

An independent board-certified radiologist rater with 2 years of experience reviewed all CTA studies independent of clinical data or other imaging studies, to determine the location of intracranial arterial stenosis or irregularity, compatible with intracranial atherosclerotic disease. The rater identified and labeled images with stenosis, with the selected images being perpendicular to the plane of the targeted lumen. After the CTA images were selected,

CTA, TOF-MRA and T_1 -weighted pre- and post-contrast IVW sequences were registered at the selected images using the automated registration tool in RadiAnt Dicom viewer (Medixant Co, Poznan, Poland). Users could manually modify the registration if the automated registration did not align correctly. The selected images in addition to one image on each side-of the selected image were included.

Two separate board-certified radiologist raters with 6 and 8 years of experience, respectively, independently reviewed the selected images for each set (MRA, IVW or CTA) while blinded to the other imaging modalities for the patient and patient clinical information. The raters measured the maximum degree of stenosis for each stenosis selected on each modality. The stenosis measurement was calculated based on the following formula: $\{1 - [D(\text{stenosis})/D(\text{normal})]\} \times 100 = \text{stenosis}$.¹⁴ $D(\text{stenosis})$ is the maximal point of stenosis, while $D(\text{normal})$ represents the normal arterial segment proximal to the stenosis, without any branching points between the normal segment and the stenosed segment. If there was no normal segment proximal to the stenosis on the ipsilateral side, the contralateral segment of the same artery was assessed. If none of these normal segment measurements could be made or stenosis involved the basilar artery, a normal segment distal to the stenosis was measured. Imaging modalities were reviewed in a random order and separate from the other imaging performed. All imaging studies were evaluated and reviewed on RadiAnt Dicom viewer (Medixant; Poznan, Poland). Luminal measurements were averaged between the two raters.

Statistics

All statistical calculations were conducted with the statistical computing language R (v. 2.14.1; R Foundation for Statistical Computing, Vienna, Austria). Throughout, two-tailed tests were used with $p < 0.05$ denoting statistical significance.

Mean stenosis and standard deviation of each imaging technique were calculated. Agreement between stenosis and lumen diameter measurements by MRA or IVW with CTA was assessed qualitatively using Bland-Altman plots. Agreement was also summarized quantitatively by the mean difference, the SD of differences and the concordance correlation coefficient (CCC).¹⁵ Generalized estimated equations (GEEs) were used to test for bias (mean difference not equal to zero). Sensitivity and specificity for $>50\%$ stenosis were estimated for MRA and IVW, using CTA as the reference. Inter-rater agreement was assessed using the CCC. The non-parametric bootstrap was used to compute 95% CIs and to compare the agreement statistics for MRA and IVW measurements. To account for the clustering of lesions, resampling was done at the patient level.¹⁶

RESULTS

Patient demographics

Eighteen total patients with 33 atherosclerotic lesions were included in the study. Of the 18 patients, 13 were imaged within 3 months of stroke, while two additional patients had strokes greater than 6 months after an ischemic event. Three patients had no history of stroke or transient ischemic attack.

Table 1. Comparison of stenosis and lumen diameter measurements by MRA and IVW MRI with CTA (reference) ($n = 33$ lesions)

Stenosis	Modality ^a		Difference			CCC	(95% CI)
	MRI	CTA	Mean	SD	<i>p</i> value ^b		
MRA, %	49 ± 25	45 ± 21	4.4	18	0.19	0.68	(0.57, 0.76)
IVW, %	45 ± 22	45 ± 21	0.1	11	0.94	0.87	(0.81, 0.92)
<i>p</i> value ^c			0.24	0.004		0.002	
Lumen Diameter	Modality ^a		Difference			CCC	(95% CI)
	MRI	CTA	Mean	SD	<i>p</i> value ^b		
MRA, mm	1.14 ± 0.65	1.05 ± 49	0.09	0.49	0.41	0.64	(0.49, 0.74)
IVW, mm	1.08 ± 0.54	1.05 ± 49	0.03	0.23	0.56	0.90	(0.81, 0.96)
<i>p</i> value ^c			0.45	<0.001	–	<0.001	

CCC, Concordance correlation coefficient; CI, Confidence interval; CTA, CT angiography; IVW, Intracranial vessel wall MRI; MRA, MR angiography; SD, Standard deviation.

^aValues are mean ± SD.

^bTest of mean difference between MRI and CTA = 0.

^cTest of difference between MRA and IVW, mean difference, SD of differences, and CCC.

No patients presented with intracranial hemorrhage. Patients had 2–6 vascular risk factors (mean: 4.1, std. dev. 1.3). The most common vascular risk factors were hypertension (17), dyslipidemia (15), and diabetes mellitus (11). Mean patient age was 53.1 years (std. dev. 10.4). Seven patients were white, 5 Hispanic, 4 Asian, 1 black, and 1 Pacific Islander. There were 6 males and 12 females in the cohort. Ten patients were receiving statin therapy, and nine patients were receiving anti-platelet agents. Only one patient had history of myocardial infarction

Segments of involvement

Arterial lesion distribution was: M1 middle cerebral artery (MCA) (14), supraclinoid internal carotid artery (ICA) (6), A1 anterior cerebral artery (ACA) (4), V4 vertebral artery, basilar artery, P1 posterior cerebral artery (PCA), A2 ACA and P2 PCA (two each), and M2 MCA (1), for a total of 33 stenotic atherosclerotic lesions.

Inter-rater agreement

The CCC between the stenosis measurements made by the 2 raters was 0.84 [95% CI (0.67–0.93)] for CTA, 0.83 [95% CI (0.67–0.93)] for TOF-MRA, and 0.85 [95% CI (0.71–0.94)] for IVW.

Comparison of stenosis measurements

Neither IVW nor MRA had any significant bias relative to CTA for stenosis and lumen diameter measurements (Table 1). IVW stenosis measurements were found to have nearly 40% lower variability ($p = 0.004$) and a significantly higher CCC (0.87 vs 0.68; $p = 0.002$) than MRA measurements with respect to the standard used, CTA (Figures 1 and 2, Table 1). Figures 3 and 4 demonstrate the corresponding Bland-Altman plots for MRA-CTA and IVW MRI-CTA stenosis comparisons, respectively, indicating a distinctly superior agreement of IVW with CTA, when compared to MRA. IVW lumen diameter measurements also had significantly higher agreement with CTA than MRA

Figure 1. 40-year-old female with right MCA territory stroke and infarct (not shown), with enhancing, eccentric atherosclerosis involving the right carotid terminus (Figure 1c, arrow). On sagittal CTA (a), there is narrowing of 60% of the right carotid terminus (arrow). On sagittal T1 IVW (b), the right carotid terminus has 58% narrowing (arrow). Sagittal T1 post-contrast IVW (c) shows an eccentric enhancing lesion with outer wall remodeling (arrow) consistent with atherosclerosis. On sagittal reconstructed 3D TOF MRA (d), there is no evidence of flow-related enhancement in the expected location of the right carotid terminus (arrow) corresponding to 100% stenosis.

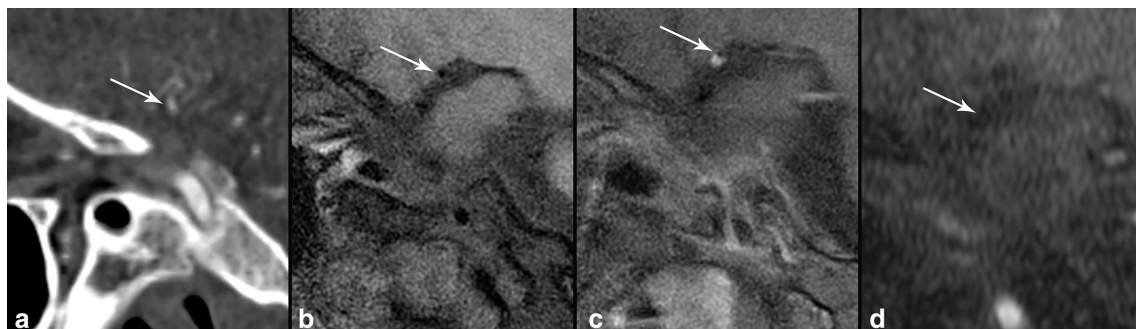
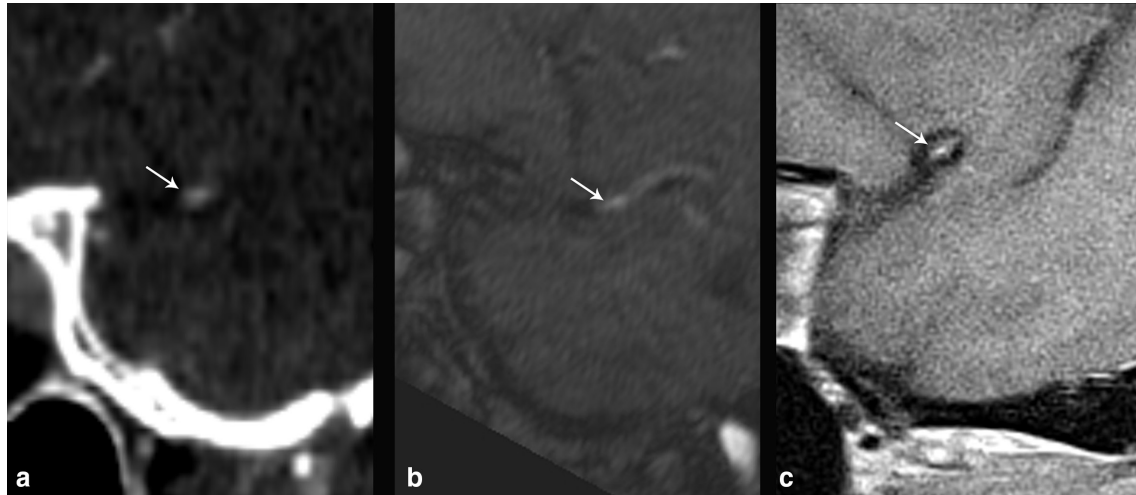


Figure 2. 53-year-old male with multiple vascular risk factors presenting with worsening dementia and multiple infarcts on CT of different stages of evolution (not shown), including right MCA territory acute infarct on MRI (not shown). CTA of the head (a) shows narrowing of the distal right M1 MCA, which measured 39% stenosis (arrow). TOF-MRA (b) showed narrowing at the same location (arrow), with 50% stenosis, while sagittal T₁-weighted IVW (c) showed atherosclerotic plaque along the superior wall of the arterial segment which showed partial enhancement (arrow), resulting in 35% stenosis, which more closely approximated the degree of stenosis seen on CTA relative to MRA.



lumen diameter measurement (CCC: 0.64 vs 0.90, $p < 0.001$; Table 1).

There were 11 lesions with stenosis >50% on CTA. Sensitivity for >50% stenosis was 64% [7/11, 95% CI (39–83%)] on MRA and 82% [9/11, 95% CI (53–95%)] on IVW. Specificity was the same for both sequences at 73% [16/22, 95% (CI 52–87%)].

DISCUSSION

Conventional luminal imaging techniques are the first-line approach to the evaluation and characterization of neurovascular disease, with TOF-MRA frequently used due to its non-invasive

nature, lack of ionizing radiation and iodinated contrast injection. Questions exist about the accuracy of luminal measurements on MRA, however. In the current study, we compared luminal measurements on TOF-MRA and IVW relative to the CTA reference standard and found significantly greater agreement between IVW and CTA compared to MRA and CTA (CCC of 0.87 vs 0.68, $p = .002$) when evaluating continuous stenosis measurements. IVW had a sensitivity of 82% compared to the MRA value of 64% while both had 73% specificity.

CTA has previously shown strong agreement in luminal measurements relative to DSA. Nguyen-Huynh et al¹⁷ compared CTA

Figure 3. Bland-Altman plot of stenosis by MRA and CTA in 33 lesions.

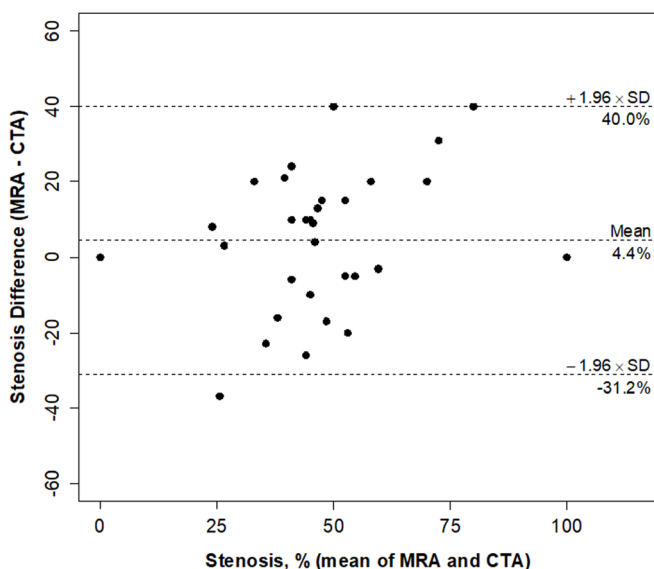
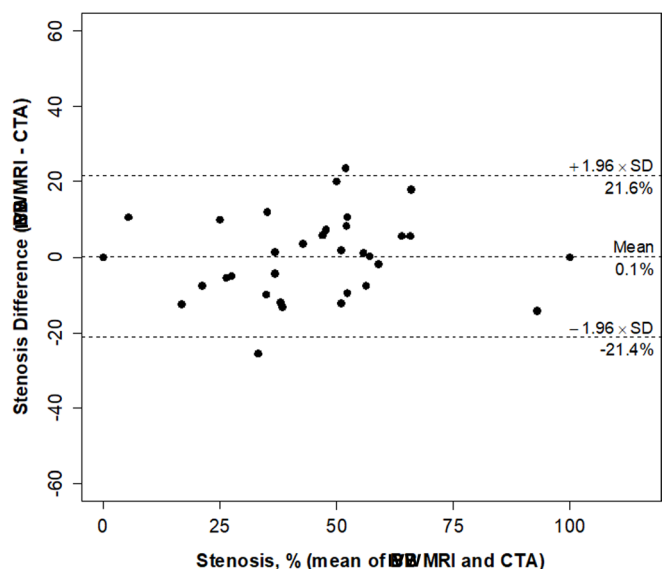


Figure 4. Bland-Altman plot of stenosis by IVW MRI and CTA in 33 lesions.



and DSA findings in 41 patients and 475 arterial segments. They found the stenosis intra-class correlation coefficient between CTA and DSA to be 0.98. CTA detected large arterial occlusion with 100% sensitivity and specificity and for detection of $\geq 50\%$ stenosis, CTA had 97.1% sensitivity and 99.5% specificity. This, in addition to the easier access, increased utilization and first-line use of CTA for stenosis evaluation justified its implementation as the reference standard in our study.

While TOF-MRA has the advantage of not exposing patients to i.v. contrast or ionizing radiation, its lower spatial resolution as compared to CTA or DSA limits its utility in smaller arterial segments. Furthermore, as a result of dependence on vascular flow for the maintenance blood signal, high-grade stenosis, turbulent or in-plane flow lead to proton spin-dephasing and downstream flow signal intensity loss. Due to these limitations, TOF-MRA has lost favor as the primary neurovascular imaging modality. The SONIA study¹⁸ found that MRA has modest correlations with DSA and concluded that abnormal findings on MRA require confirmation with DSA.

There are a few published studies evaluating the accuracy of IVW for luminal measurement assessment relative to other luminal imaging modalities. Liu et al¹⁹ compared 2D T_2 -weighted black blood imaging with CTA against 2D DSA for the evaluation of MCA steno-occlusive disease in 28 patients. IVW-derived stenosis values correlated better with DSA (Spearman correlation $R = 0.68$, $p = 0.01$) than CTA MIP or VR reconstructions (Spearman correlation $R = 0.45$, 0.22 ; $p = 0.02$, 0.24 , respectively). In 10 patients with large vessel occlusion, Hui et al²⁰ compared findings of pre- and post-contrast T1 IVW with 3D-TOF-MRA and 2D DSA. Apart from 10 occluded vessels in which there was full agreement among all imaging methods, IVW showed seven other stenotic vessel segments versus only two demonstrated by MRA and DSA. IVW showed a higher frequency of wall abnormalities (thickening and enhancement) compared with DSA and MRA ($p = 0.016$ and $p = 0.008$, respectively). Lee et al²¹ compared 2D pre- and post-contrast IVW with 3D DSA in 37 patients, and found moderate-to-excellent agreement (interclass correlation coefficient = 0.892 – 0.949 ; $K = 0.548$ – 0.614) and significant correlations ($R = 0.766$ – 0.892) between IVW and DSA on the degree of stenosis and minimal luminal diameter. The inter-observer diagnostic agreement was good for DSA ($K = 0.643$) and excellent for IVW ($K = 0.818$). Park et al²² also compared 3D IVW with 2D DSA in 43 patients and found a similar degree

of stenosis ($p > .05$) and higher luminal diameter ($p < .05$) on IVW compared to DSA. Kim et al²³ evaluated 286 segments in 17 patients with both IVW and MRA, for stenosis and atherosclerosis presence, with IVW as the reference standard for atherosclerosis presence and MRA as the reference standard for luminal stenosis. IVW had a 92.5% sensitivity and 82.1% specificity for stenosis relative to MRA, while MRA had a sensitivity of 59.4% and a specificity of 98.3%, respectively, relative to IVW. This study shows the value of IVW for stenosis measurements, however, the current and other studies demonstrate limitations of MRA in stenosis assessments. Bai et al²⁴ developed a luminal imaging technique from IVW acquisitions and found this new technique showed significantly higher sensitivity for detection of severe stenosis (89.3% vs 64.3%, $p = .039$) relative to MRA and comparable to the sensitivity of IVW. The results of the present study are in line with the above-discussed literature suggesting superior correlation of IVW with the reference standard test for the evaluation of steno-occlusive disease; however, this study is the only one to compare stenosis measurements on IVW and MRA relative to the front-line imaging modality for intracranial stenotic disease, CTA.

There are several limitations with the current study, including retrospective study design and limited number of subjects. Studies with larger cohorts and lesion counts, additional readers and evaluating varied luminal techniques are needed to further validate these findings. The study also utilized 2D-IVW techniques, although only lesions involving arteries coursing perpendicular to the plane of imaging were included in order to minimize volume averaging and wall thickness overestimation effects. Further comparisons with additional IVW techniques is necessary to also confirm these findings, as these results may differ with technique differences.

CONCLUSION

IVW can more accurately assess atherosclerotic luminal measurements relative to TOF-MRA, as compared to CTA. TOF-MRA is frequently performed as part of IVW protocols, for rapid identification of intracranial stenosis; however, these stenoses should be confirmed with IVW, and IVW can be used to quantify more accurately the degree of stenosis.

FUNDING

R01 NS092207, R56 NS092207, R00HL136883

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