Title

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Yuting Wang[1,2], **Xinke Liu**[2,3], **Henrik Haraldsson**[2], **Chengcheng Zhu**[2], **Megan Ballweber**[2], **Warren Gasper**[4], **Thomas Hatsukami**[5], **David Saloner**[2]

[1]Department of Radiology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, No. 2006 Xiyuan Avenue, Chengdu 611731, China

[2]Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA

[3]Department of Interventional Neuroradiology, Beijing Neurosurgical Institute and Beijing Tiantan Hospital, Capital Medical University, Beijing, China

[4]Division of Vascular and Endovascular Surgery, University of California, San Francisco, CA, USA

[5]Department of Surgery, University of Washington, Seattle, WA, USA

Abstract

Objectives—This study aims to evaluate the reproducibility of measures of plaque morphology in serially acquired black-blood MRI of untreated atherosclerotic femoral arteries.

Materials and methods—MR studies was obtained from 42 timepoints, on 12 patients with known femoral artery atherosclerosis. Images with a 3D isotropic FLASH with DANTE-prepared black blood contrast (DASH) at a 3-T scanner were acquired at baseline, within 1 week, and at 1 month. Six of the patients were scanned additionally at 6 months. Inter-scan and inter-observer variations of arterial area/volume measurements were evaluated.

Results—Measurement of vessel area, lumen area, wall area and wall volume showed inter-scan intraclass correlation coefficients (ICC) ranging from 0.92 to 0.97 for 3 scans, 0.91–0.97 for 4 scans, and inter-observer ICCs of 0.89–0.96. Among 3 scans, the coefficients of variance (CV) for the vessel area, lumen area, wall area and wall volume were 4.1%, 6.5%, 7.5%, and 4.4%. CVs among 4 scans ranged from 4.4% to 7.9%, and interobserver CVs ranged from 6.1% to 11.8% for the different area/volume measurements.

Conclusion—DASH MRI is useful for quantifying atherosclerotic vessel area and volume of femoral arteries with low variability among serial repeated scans and between observers.

Keywords

Black blood; MR; Femoral; Atherosclerosis; Reproducibility

Introduction

Peripheral artery disease (PAD) is a serious health issue worldwide, affecting about 27 million people in North America and Europe [1, 2]. Patients with PAD have a two- to threefold increased risk of stroke and fivefold increased risk of heart attack, and attendant higher mortality [3]. The major cause of PAD is atherosclerosis, a systematic arterial wall disease that gradually narrows the arteries and obstructs blood flow, resulting in intermittent claudication, critical extremity ischemia, and even amputation [4-6]. Although critical luminal stenosis has been proposed as the most important diagnostic imaging marker, in most progressing lesions luminal narrowing typically lags behind arterial wall thickening because of positive outer wall remodeling [7-9]. Atherosclerotic plaques may either progress or regress over time, depending on individual risk factors and treatment options (supervised exercise, pharmacotherapy, endovascular and open surgical revascularization) [7, 10]. An ability to directly depict arterial wall morphology is essential, not only for early detection and serial monitoring of PAD, but importantly to elucidate the response to intervention. A fundamental question in determining temporal change in plaque burden is a determination of measurement error—change is only meaningful if it exceeds the error of measurement.

Conventional luminal imaging such as CTA, MRA, and DSA cannot provide information on vessel-wall thickening. High-resolution MR imaging with black-blood technology has emerged as a noninvasive imaging modality for direct and quantitative assessment of vessel-wall thickness and plaque burden, and additionally for sensitive monitoring of treatment response in a short time [11-13]. Although 2D black-blood fast spin-echo acquisition has been extensively used for vessels such as carotid and coronary arteries [14, 15], it is unsuited for femoral artery evaluation as a much greater coverage is required in the lower extremities [16]. Recently, DANTE (Delay Alternating with Nutation for Tailored Excitation), a method for improved black-blood preparation [17, 18], was proposed as a suitable method for assessing the femoral vessel wall, mainly because of its relative insensitivity to B1 field inhomogeneity and independence on inflow effects [19]. However, the reproducibility of this novel DANTE-prepared 3D FLASH (DASH) sequence for evaluating atherosclerotic femoral artery has not been established. The earlier study investigating reproducibility of qualifying atherosclerotic plaques of femoral arteries relied on multi-slice 2D turbo-spin-echo pulse sequence on a 1.5-T scanner [9]. The 3D technique on 3-T scanners has made considerate improvement with higher resolution, shorter acquisition time and better blood signal suppression [19]. The study that validated the 3D DASH sequence in femoral arteries limited the investigation to in vitro simulations, 8 healthy volunteers, and only 3 patients who did not follow the typical patient selection process in clinical practice. In addition, it did not measure the scan–rescan reproducibility [19]. Other studies that employed black-blood MR techniques to measure femoral arteries did not use DANTE preparation to suppress flow signal or use dual lumen-contrast to differentiate lumen from adjacent calcification, and lacked of scan-rescan data for a more thorough evaluation of reproducibility [16,

20]. Another study exploring dual lumen-contrast to improve the measurement of femoral atherosclerosis did not have scan–rescan data either [21]. In determining whether there has been a meaningful change in vascular morphology over time, particularly in response to novel therapies, it is essential to compare that change to the expected error of measurement, and this study, therefore, aims to more comprehensively evaluate the inter-scan and inter-observer reproducibility of 3D DASH MRI at 3 T for atherosclerotic femoral arterial wall measurement in multiple serial follow-up MR scans in a PAD patient cohort.

Methods

Study population

The institutional review board of our medical center approved this prospective study and written consent was obtained from each patient. The patient cohort was from a registered prospective clinical trial: Intima Versus Adventitia Drug Delivery to Elucidate Mechanisms of Restenosis: Magnetic Resonance Imaging (INVADER, https://clinicaltrials.gov/ct2/show/NCT02807779), exploring novel endovascular therapies for occlusive PAD as evaluated by MRI. It prospectively recruits patients with clinically diagnosed atherosclerotic PAD with the following criteria to represent the patient population of femoral atherosclerosis. Inclusion criteria: (1) male or non-pregnant female   35 years of age; (2) with clinically diagnosed atherosclerotic PAD; and (3) the target leg has stenosis (but no occlusion) detected by MRI that in the clinician's opinion is the reason for the PAD symptoms. Exclusion criteria: (1) any contraindication to receiving an MRI; (2) previous surgical or interventional procedure of the target lesion; (3) history of hemorrhagic stroke within 3 months; (4) chronic renal insufficiency with eGFR < 30 mL/min/1.73 m^2; (5) acute limb ischemia; and (6) patient is receiving long-term oral steroids for unrelated condition.

Atherosclerosis is a systemic disease, and all patients in the study demonstrated bilateral atherosclerosis of femoral arteries. In this report of reproducibility, we focus on femoral artery analysis of the leg with nonocclusive PAD where no treatment was performed.

In the INVADER study, patients undergo three MR imaging studies in the first month following enrollment. Reproducibility was assessed for those three studies as it is expected that changes in plaque features are expected to be undetectable on MR imaging over this relatively short time period, and any difference in measurement could then be ascribed to measurement error. In addition, possible morphology changes of the leg with nonocclusive atherosclerosis was studied in patients who had also completed imaging at the 6 months' time point.

Image acquisition

The subjects underwent MR imaging at 3 or 4 time points: (1) at baseline; (2) within 1 week; (3) at 1 month, and for 6 of the patients, at (4) six months. All patients underwent MRI using a 3-T MRI system (Siemens Skyra, Siemens Health¬care, Erlangen, Germany) using a 36-channel peripheral coil placed on top of the legs and used in combination with a 32-channel spine coil.

From prior imaging, the treating surgeon estimated the site of the location and the estimated distance, d_{est}, of that lesion from the medial tibial spine in the knee which served as a fiducial marker for MR scan localization. At all imaging sessions, a gradient echo scout was first performed to localize the tip of the medial tibial spine at the knee. The table was then moved to place the medial tibial spine at the distance, d_{est}, from the isocenter, which assured that the target lesion was then at isocenter in the magnet. Low-quality and sparse 2D TOF scout images were then acquired over a 50-cm length to identify the course of the femoral arteries. DASH and MPRAGE volumetric data sets were acquired in the identical coronal orientation with the acquisition slab rotated to align with the course of the femoral artery as determined from the TOF images.

DASH parameters were: flip angle = 12°, pulse train length = 100, TR = 1055 ms, TE = 3.5 ms, resolution = $0.8 \times 0.8 \times 0.8 mm^3$, longitudinal coverage = 370 mm, bandwidth = 189 Hz/pixel, 75% partial Fourier in both phase and slice direction, DANTE-preparation 150 RF pulses a 15° flip angle with 0.61 ms gradient applied in readout, phase and slice direction resulting in a net gradient of 41.2mT/m. Neither parallel imaging nor averages were used for the acquisition. The acquisition time for DASH was close to 6 min.

Parameters for MPRAGE were: flip angle = 11°, pulse train length = 224, TR = 1780 ms, TE = 3.1 ms, resolution = $1.0 \times 1.0 \times 0.8 mm^3$, longitudinal coverage = 360 mm, bandwidth = 320 Hz/pixel, parallel imaging using GRAPPA with an acceleration factor of 2, inversion time 900 ms. The acquisition time for MPRAGE was close to 5 min.

Image analysis

All images were transferred to an offline workstation, and analysis was performed with image postprocessing software (Horos, 3.3.5). Image quality was assessed on a subjective 5-point rating by consensus of two radiologists (with 6 years and 2 years of vascular MRI experience, respectively): 1, non-diagnostic due to poor vessel-wall delineation; 2, vessel-wall boundary identification difficult due to poor blood suppression, motion artifacts and/or local wall signal voids; 3, moderate ability to delineate vessel wall due to slightly inadequate blood suppression and/or artifacts; 4, good vessel-wall depiction with adequate blood suppression and homogeneous wall signal; and 5, excellent vessel-wall delineation with high contrast of hyperintense vessel wall and artifact-free hypo-intense lumen, yielding sharp edges. Only studies with image quality of at least 3 points were included.

To avoid any measurement bias due to the difference in location, internal vascular fiducials such as arterial bifurcation, small branch orifices, focal calcification of arterial wall, and adjacent venous valve were used to bring arterial segments from consecutive data sets into co- registration. In each subject, 15 continuous 0.8-mm-thick, cross-sectional images were reformatted transverse to the non-occluded femoral artery segment and centered on the isocenter of the acquisition [19]. To differentiate vessel lumen and vessel surface, cross-sectional images of DASH sequence were compared with MPRAGE studies to identify juxtalumenal calcification—commonly occurring in arteriosclerotic femoral arteries—which might otherwise be included as part of the lumen on black-blood imaging. An area with signal void on both DASH (black blood presentation) and MPRAGE (gray-blood presentation) was designated as calcification and was not included in the lumen area

measurement. On the contrary, an area with hypointensity on DASH but intermediate signal on MPRAGE was designated as lumen, as shown in Fig. 1. The two readers then independently performed manual freehand contouring of vessel area and lumen area on each slice of the DASH after a consensus approach to image interpretation was formed using a training set of 60 images. Wall area was calculated by subtraction of lumen area from vessel area. Wall volume was calculated by summation of wall area of the continuous 15 slices multiplied by 0.8-mm thickness (Fig. 2).

Statistical analysis

Statistical analyses were performed using SPSS (v.19.0; SPSS, Chicago, IL, USA) statistical software. Inter-scan and inter-observer agreement was measured by the intraclass correlation coefficient (ICC) with 95% confidence intervals (CIs). ICC values of less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 were defined as poor, moderate, good, and excellent reliability, respectively [22]. Measurement error was quantified by slice-based (area) or patient-based (volume) coefficient of variance (CV, CV = pooled variance/ mean × 100%). Pooled variance was used to combine the variances for the individual slices to account for geometric differences between patients as well as along the vessel. Slice-based (for area) or patient-based (for volume) paired t-test was employed where appropriate. A p value of < 0.05 was used to indicate statistical significance. Differences between areas/volumes measurement by two observers were assessed using the Bland–Altman analysis showing ± 1.96 × standard deviation range [23]. To inform future studies of serial morphology changes, the sample sizes needed to detect 5%, 10%, 15% and 20% changes in vessel area/volume were calculated using 90% power and 5% significance level [24].

Results

From 2016 February to 2019 April, 26 patients with known atherosclerosis of femoral arteries in total were enrolled in this prospective study. Two patients withdrew from the study. Ten patients had only one scan (three are still in ongoing follow-up; three were transferred to a different endovascular therapy and no longer conform to the INVADER criteria; two had circumferentially calcified arteries preventing catheterization; in one, the femoral artery disease was too diffuse; and one had the intervention and corresponding follow-up scans suspended), two patients had one timepoint with image quality score of 2 points, and, therefore, were excluded.

Finally, twelve patients with MR scans of 3 timepoints (baseline, within 1 week, at 1 month) were included in the analysis. Of these, six patients also had an additional scan at the 4th timepoint (at 6 months.) Of the twelve patients, eleven were men ranging in age from 59 to 88 years old (mean: 70 years old), BMI from 16.8 to 43.6 (mean: 25.4). Eleven patients had hypertension, and seven patients had diabetes. Six patients showed segmental atherosclerotic plaques along the femoral artery, and six patients exhibited diffuse atherosclerotic femoral arteries. No occlusive femoral arterial segments were identified in the included patients.

In total, MR scans were performed at 42 timepoints and analyzed. Table 1 summarizes the results of inter-scan reproducibility for atherosclerotic femoral arteries with the DASH

sequence. All of the morphologic measurements had ICCs greater than 0.90, indicating excellent agreement among scans at different timepoints. The pooled CV was largest for wall area measurement, and was slightly bigger among 4 timepoints than among 3 timepoints. The CV of volume measurement was generally smaller than that of area measurements.

In total, measurements were made of 630 slices by each of the two observers and were compared pairwise. Table 2 exhibits the results of inter-observer reproducibility for atherosclerotic femoral arteries using the DASH sequence. Again, excellent agreement was achieved with all ICCs greater than 0.89. All measurements showed no statistical bias apart from the lumen area where areas measured by one reviewer are slightly larger than by the other (by 2.3% of mean values). Relatively small CVs were identified for both area (6.1–11.8%) and volume measurements (6.6%). In accordance with inter-scan variance, wall area measurement had the largest variation, and volume measurement tended to have smaller variance compared to area measurements. Bland–Altman plots for vessel area, lumen area, wall area and wall volume measurement of the two observers are shown in Fig. 3. A dispersed distribution pattern of measurement error was observed.

The change of arterial morphological parameters over 1 month and 6 months was also investigated, and the results are summarized in Table 3. No significant change of arterial area/volume was identified between baseline and 1 month. The vessel area increased by 2.2%, and the wall area increased by 3.5% over 6 months, both with statistical significance. However, the lumen area did not change significantly. Arterial wall volume had only 5 paired measurement after 6 months, and significant differences were not detected.

Sample size calculation for detecting 5–20% change in vessel area and volume are presented in Table 4. CV among 3 scans was used for calculation given the statistically stable disease condition. The results indicate that given the measurement CV established from the three scan studies, it would be necessary to recruit 52 subjects if the interventional treatment effect size was 5% but that only 13 subjects would be needed if the effect size was 10%. In general, the adoption of volume measurement as an outcome measure would require smaller sample sizes compared with area measurements.

Discussion

The measure of reproducibility is crucial for implementing the novel 3D DASH technique in the clinical setting and for consideration in future applications. In this study, patients with known atherosclerosis of femoral arteries were prospectively and serially scanned at multiple standardized time points with a DASH sequence at 3.0 T, and isotropic high-resolution vessel-wall imaging with large coverage was achieved. The study design provided a rare opportunity to evaluate an extended territory of atherosclerotic disease with more than two studies in a time interval that was short relative to the typical temporal evolution of atherosclerosis. As such, it provides a unique clinical data set for establishing measurement error—a key metric in determining response to therapy. Both inter-scan and inter-observer reproducibility were demonstrated for quantification of arterial wall thickening, with excellent agreement measured by ICC, and relatively low variation measured by CV. Slight

but statistically significant progression of wall thickening was observed after 6 months of follow-up. Sample size estimation was provided for future studies to monitor femoral arterial plaque burden changes—changes that could result from natural progression, or in response to novel surgical or pharmacological intervention therapies, as in the INVADER trial.

Technical challenges and solutions

Major challenges for black-blood MR for peripheral vessel-wall imaging include relatively slow blood flow which reduces the black blood effect; and a requirement of extended longitudinal coverage while simultaneously preserving spatial resolution [16]. DANTE showed favorable flow signal suppression even in stenotic femoral arteries with slow blood flow. This is demonstrated in Fig. 2 where both arterial and venous blood flow were completely suppressed. DANTE is also suitable for large longitudinal coverage because of its insensitivity to B1 field inhomogeneity due to the use of low-flip-angle radio-frequency pulses [19]. With the time-efficient 3D FLASH readout, DASH allowed a longitudinal coverage of 370 mm and isotropic resolution of 0.8 mm within 6 min, with generally good image quality (score > 3) and measurement reproducibility in this study. One potential pitfall of this sequence, however, is the inability to differentiate the arterial lumen and adjacent calcification of the wall, since both present as a signal void (black), and diffused calcification is common in arteries of lower extremities. This limitation can be overcome by reviewing the MPRAGE study, which yields gray-blood images and, thus, provides dual lumen-contrast.

Implementation of different measurements

In this study, lumen area measurement had the largest variation among the area measurements in the slice-based pairwise analysis. Possible reasons for this include: focal artifacts caused by inadequate blood suppression; slight differences in lumen delineation by observers when small branches arose; relatively small size of the lumen; and more irregularity of the lumen compared to relatively smooth outer edges of the vessel. In addition, in delineating the outer wall, the satisfactory fat saturation enabled a relatively clear depiction of vessel outer borders. Both the ICC and CV showed better repeatability of DASH for volume measurement than area measurements, possibly given that differences between slices tended to average out, yielding a more stable measurement.

Monitoring the progression/ regression of atherosclerotic burden

Monitoring the progression and regression of atherosclerotic lesions is of great clinical concern. Studies indicate that MRI can noninvasively and accurately evaluate the effects of drugs and/or mechanical treatments, such as statins or balloon angioplasty, in multiple vascular beds [25, 26]. The remarkable rate of restenosis after revascularization procedures also demands early and accurate monitoring of lesion changes [27]. This study, with standard follow-up intervals of 1 week, 1 month and 6 months showed that the atherosclerotic wall area/volume of femoral arteries had no significant change at 1 month, but had increased by 3.5% at 6 months in the condition of no intervention. A previous study reported 5.2% increase of femoral vessel-wall area at 1 year [28], and our finding at 6 months presents an earlier timepoint where significant change might have occurred. Although the sample size of 12 may not be sufficient to accurately detect area/volume

change of 3.5%, this observation could be further validated in trials with larger sample sizes. Our study also provides a power calculation to aid future trials that aim at examining atherosclerotic plaque burden changes between two timepoints.

Limitations

There are several limitations of our study. First, included patients are predominately male ($n = 11$), because of the institutional practice conditions in the Veterans Affairs healthcare system. Second, despite consensus training, bias still existed in terms of lumen area measurement between the two observers. This is likely a result of the ambiguous appearance of the luminal boundary on DASH which results from factors such as focal, likely flow-related, artifacts. Third, two patients had unsatisfactory image quality for at least one timepoint and were excluded. Possible reasons include uncontrolled motion because of pain, and complicated hemodynamic changes induced by PAD.

In conclusion, high-resolution DANTE-FLASH MRI is useful for quantifying atherosclerotic vessel area and volume of femoral arteries with low variability among serial repeated scans and between observers. We estimate that a sample size of 52 subjects would be needed to detect an effect size of 5% change in vessel volume. Volume measurement tends to be more reproducible than vessel-wall area measurements.

Funding

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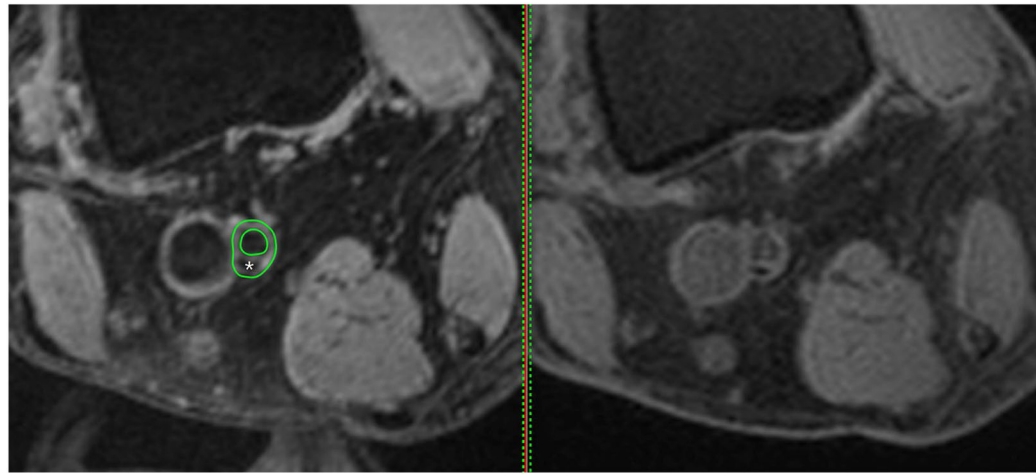
Fig. 1.
Identification of femoral arterial lumen boundary. Boundaries on DANTE-prepared 3D FLASH (left) were depicted with differentiation from juxtalumenal calcification (star mark) on MPRAGE (right)
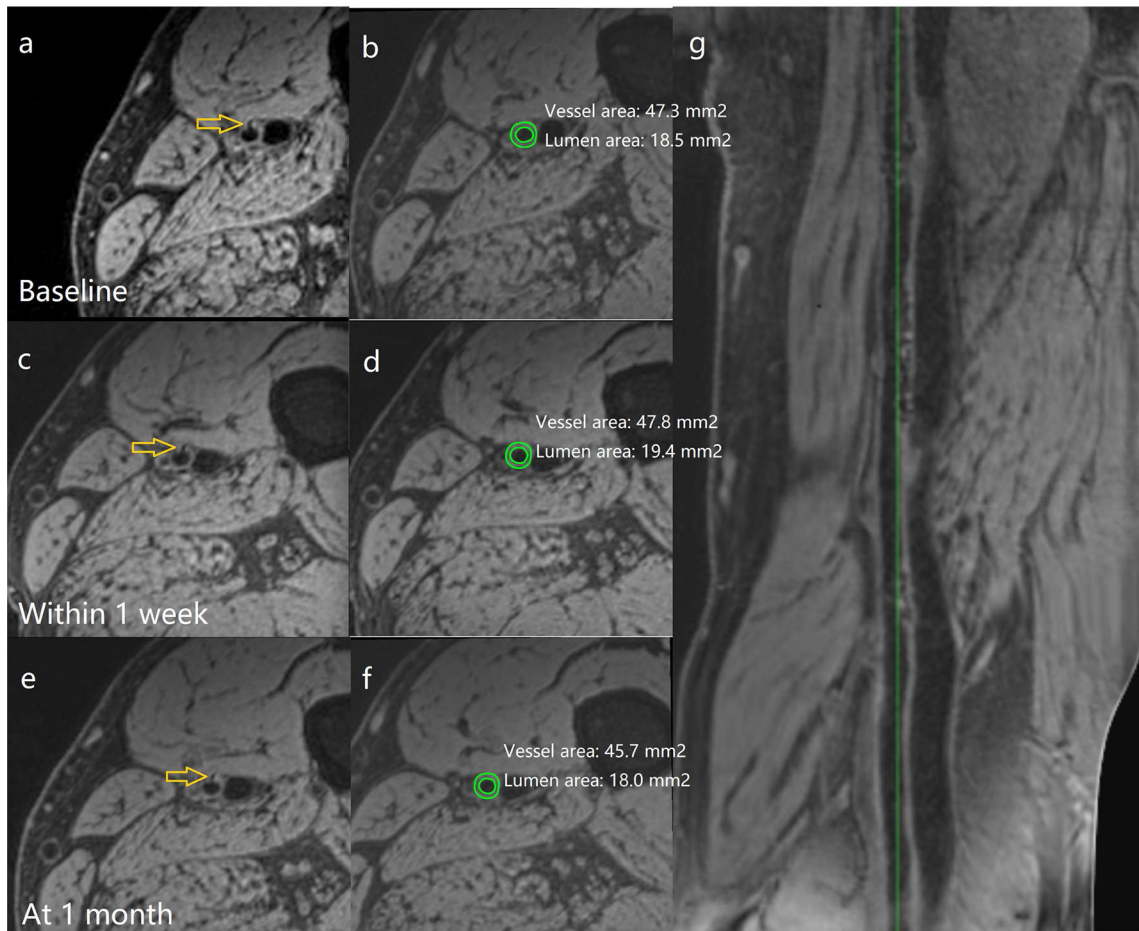
Fig. 2.
Measuring vessel and lumen area changes at different time-points using DANTE-prepared
3D FLASH. **a**, **c**, **e** Show the method for strict registration of arterial segment levels by
internal fiducials as shown by the arrows (branch opening). **b**, **d**, **f** Show the delineation of
vessel and lumen areas. Multiplanar reconstruction of the longitude coverage of the femoral
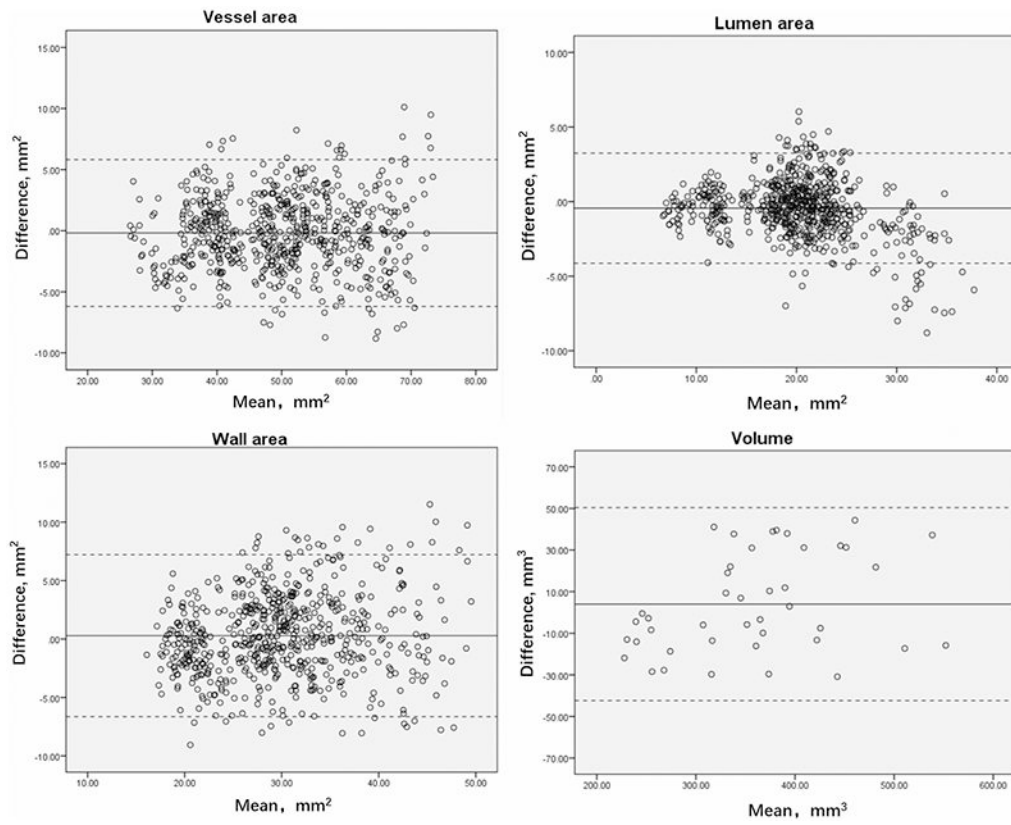artery is shown in (**g**)

Fig. 3.
Bland–Altman plot of area and volume measurements between two observers. Solid lines represent the mean difference, and dashed lines represent the 95% limits of agreement

Table 1

Inter-scan reproducibility for vessel measurements in patients with atherosclerotic femoral arteries by DASH sequence

	Among 3 timepoints (12 patients)			Among 4 timepoints (6 patients)		
	Mean	Pooled CV	ICC (95% CI)	Mean	Pooled CV	ICC (95% CI)
Vessel area (mm²)	49.18	4.1%	0.96 (0.94,0.97)	53.23	4.4%	0.96 (0.95,0.97)
Lumen area (mm²)	19.71	6.5%	0.96 (0.95,0.97)	20.81	7.9%	0.92 (0.90,0.95)
Wall area (mm²)	29.41	7.5%	0.92 (0.89,0.93)	32.41	7.9%	0.91 (0.88,0.94)
Volume (mm³)	360.2	4.4%	0.97 (0.92,0.99)	386.6	5.1%	0.97 (0.89,0.99)

Table 2

Inter-observer reproducibility for vessel measurements in patients with atherosclerotic femoral arteries by DASH sequence

	Mean-obs1	Mean-obs2	CV	Bias (*P* value)	ICC (95% CI)
Vessel area (mm^2)	49.86	50.05	6.1%	No (0.13)	0.96 (0.95, 0.97)
Lumen area (mm^2)	19.84	20.32	8.7%	Yes (< 0.01)	0.94 (0.94, 0.95)
Wall area (mm^2)	30.02	29.73	11. 8%	No (0.07)	0.89 (0.87, 0.90)
Volume (mm^3)	360.4	357.6	6.4%	No (0.28)	0.96 (0.93, 0.98)

Obs observer, *ICC* intraclass correlation coefficient

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Table 3

Changes of wall thickening over time

	Baseline vs. 1 month later (12 patients)				Baseline vs. 6 months later (6 patients)			
	Mean at baseline	Mean at 1st month	P value	Change	Mean at baseline	Mean at 6th month	P value	Change
Vessel area (mm^2)	49.0	49.2	0.21	0.4%	52.7	54.0	< 0.001	2.2%
Lumen area (mm^2)	19.8	20.0	0.10	1.0%	21.1	21.2	0.75	0.4%
Wall area (mm^2)	29.2	29.2	0.92	< 0.1%	31.7	32.8	< 0.001	3.5%
Volume (mm^3)	350.9	350.9	0.99	< 0.1%	380.1	393.4	0.16	3.5%

Table 4

Sample size calculation

	CV	5%	10%	15%	20%
Vessel area	4.4%	16	4	2	1
Lumen area	7.9%	52	13	6	3
Wall area	7.9%	52	13	6	3
Volume	5.1%	22	5	2	1