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Insufficient slow-flow suppression mimicking aneurysm wall enhancement in magnetic resonance vessel wall imaging: a phantom study

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OBJECTIVE MR vessel wall imaging (VWI) is increasingly performed in clinical settings to support treatment decision-making regarding intracranial aneurysms. Aneurysm wall enhancement after contrast agent injection is expected to be related to aneurysm instability and rupture status. However, the authors hypothesize that slow-flow artifacts mimic aneurysm wall enhancement. Therefore, in this phantom study they assess the effect of slow flow on wall-like enhancement by using different MR VWI techniques.

METHODS The authors developed an MR-compatible aneurysm phantom model, which was connected to a pump to enable pulsatile inflow conditions. For VWI, 3D turbo spin echo sequences—both with and without motion-sensitized driven equilibrium (MSDE) and delay alternating with nutation for tailored excitation (DANTE) preparation pulses—were performed using a 3-T MR scanner. VWI was acquired both before and after Gd contrast agent administration by using two different pulsatile inflow conditions (2.5 ml/sec peak flow at 77 and 48 beats per minute). The intraluminal signal intensity along the aneurysm wall was analyzed to assess the performance of slow-flow suppression.

RESULTS The authors observed wall-like enhancement after contrast agent injection, especially in low pump rate settings. Preparation pulses, in particular the DANTE technique, improved the performance of slow-flow suppression.

CONCLUSIONS Near-wall slow flow mimics wall enhancement in VWI protocols. Therefore, VWI should be carefully interpreted. Preparation pulses improve slow-flow suppression, and therefore the authors encourage further development and clinical implementation of these techniques.

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KEYWORDS intracranial aneurysms; vessel wall imaging; slow flow

For patients with multiple aneurysms and an acute hemorrhagic stroke, it is important to identify the ruptured aneurysm. Aneurysm rupture status cannot always be determined based on the bleeding pattern alone. Aneurysm size[4] and morphology[2] can help in decision-making, but additional characteristics are required to improve the identification of ruptured aneurysms.

Vessel Wall Imaging

Aneurysm wall assessment using MR vessel wall imaging (VWI) is increasingly performed to identify ruptured or unstable aneurysms.[11,12] MR VWI enables aneurysm wall assessment by suppressing MR signal originating from flowing blood and CSF. 3D turbo spin echo (TSE) is a commonly used VWI technique, which mainly suppresses flow in the readout direction.[14] Because intracranial blood flow is often complex (slow, stagnant, or turbulent), preparation pulses have been developed to optimize flow suppression. Commonly used preparation pulses are motion-sensitized driven equilibrium (MSDE) and delay alternating with nutation for tailored excitation (DANTE).[7,17,18]

Aneurysm wall enhancement after Gd contrast agent injection is suggested to be related to inflammation in

ABBREVIATIONS bpm = beats per minute; DANTE = delay alternating with nutation for tailored excitation; MCA = middle cerebral artery; MSDE = motion-sensitized driven equilibrium; TSE = turbo spin echo; VENC = velocity encoding; VWI = vessel wall imaging; WSS = wall shear stress.

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unstable aneurysm walls.[6] However, the performance of blood suppression in VWI decreases after Gd contrast agent injection, because Gd shortens the T1 relaxation time of blood. A hyperintense appearance originating from unsuppressed blood could therefore potentially be mistaken for aneurysm wall, which is an important pitfall of MR VWI.[5,8] The aim of this phantom study was to assess the contribution of slow flow to wall-like enhancement in 3D TSE VWI, both with and without MSDE and DANTE preparation pulses.

Methods

Phantom Development

We developed an MR-compatible aneurysm phantom model based on a stable middle cerebral artery (MCA) aneurysm (6 mm) from a patient who was studied with 7-T MR VWI (Fig. 1) The 7-T time-of-flight MR angiography data were used to segment the aneurysm and perianeurysmal vasculature by using a level set segmentation algorithm from the Vascular Modeling Toolkit (http://www.vmtk.org). Subsequently, the 3 outflow vessels were manually connected using open-source 3D modeling software (Blender version 2.74, http://www.blender.org/). A 3D printer (Connex3 Objet260; Stratasys) was used to print a hollow vessel lumen in a solid plastic box. VeroClear, a transparent polymer, was used as printing material. The benefit of such a polymer is that it does not get magnetized during the MRI session, and therefore appears black in VWI. Finally, inflow and outflow tubes were connected to the 3D-printed model, and then the model was submerged in an agar solution to obtain a homogeneous local magnetic field. Figure 2 demonstrates the phantom development pipeline.

MRI Experiments

In Fig. 3, a schematic overview of our MR phantom experiment setup is presented. MRI acquisitions were performed using a 3-T Ingenia MR scanner (Philips Healthcare) and a 32-channel head coil. The phantom was connected to a pump outside the scanner room to generate pulsatile inflow conditions. We used water to pump through the phantom model and performed 2D phase-contrast MRI (resolution 0.38 × 0.38 × 3 mm; TE/TR 6.9/15.7 msec; flip angle 25°; velocity encoding [VENC] 80 cm/sec; 26 cardiac phases) perpendicular to the parent vessel to measure the inflow waveform. For pulsatile inflow conditions, we generated a peak flow of approximately 2.5 ml/sec, which is comparable to physiological MCA inflow.[3] Pump rates of 77 and 48 beats per minute (bpm) were used to simulate different intra-aneurysmal flow conditions: peak flow ve-

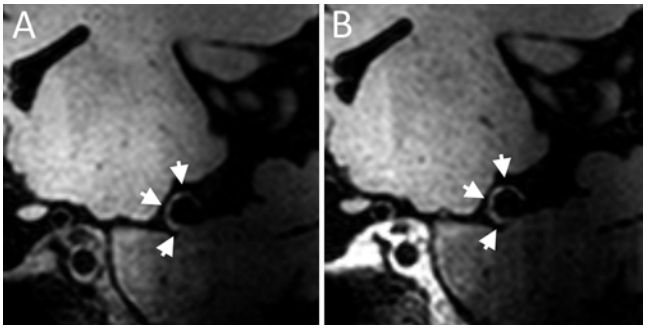

FIG. 1. 7-T MR VWI before (**A**) and after (**B**) contrast agent administration, acquired in a patient harboring a stable MCA aneurysm. The *white arrows* indicate the aneurysm wall.

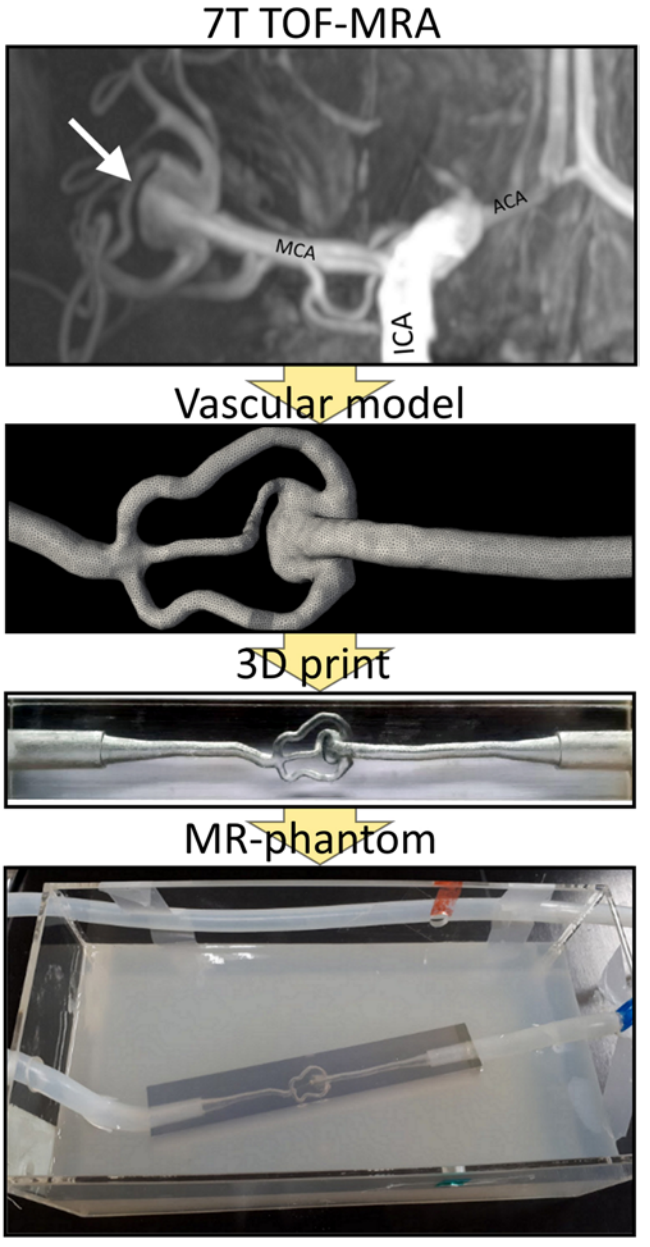

FIG. 2. Phantom model development pipeline, based on 7-T time-of-flight (TOF) MR angiography patient data. Level set segmentation was performed to isolate the aneurysm (*white arrow*) and inflow/outflow vessels. The outflow vessels were connected using 3D modeling software. The vascular model was 3D printed as a hollow vessel lumen in a solid plastic box. To finalize the phantom, in- and outflow tubes were connected to the 3D printed model, and then the model was submerged in an agar solution. ACA = anterior cerebral artery; ICA = internal carotid artery.

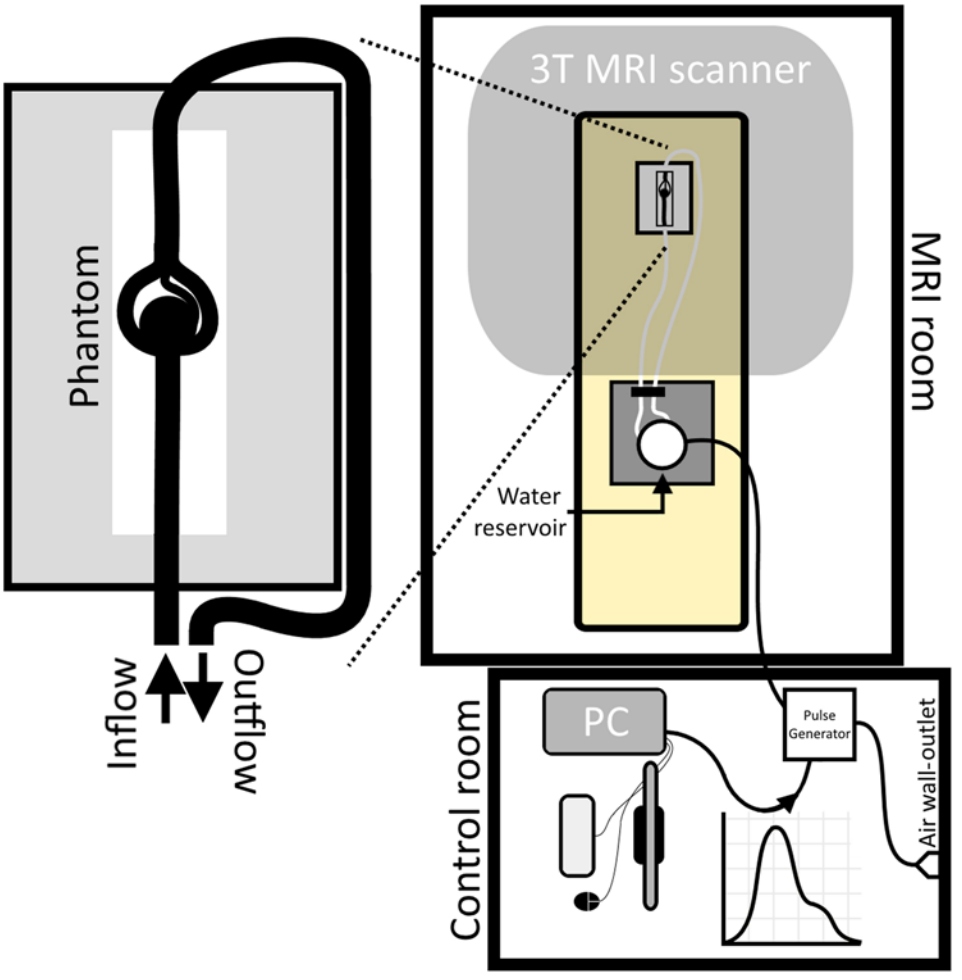

FIG. 3. Schematic overview of the MR experiment setup. The phantom and pump reservoir were situated in the MRI room. The reservoir was connected to the pump in the control room, which was controlled by a desktop computer (PC) to generate pulsatile inflow conditions.

locities remained similar, but average velocities were different in both settings.

VWI was performed before and after Gd (gadobutrol, Gadavist; Bayer BV) enhancement. Based on the drug description, gadobutrol is rapidly distributed in plasma: 2 minutes after administration the in vivo plasma concentration is 0.59 mmol/L, 60 minutes after administration the plasma concentration is 0.3 mmol/L. Assuming exponential distribution dynamics and VWI acquisition 15 minutes after venous contrast injection, we estimate the concentration to be approximately 0.4 mmol gadobutrol per liter of plasma in clinical settings. Therefore, for our contrast-enhanced phantom experiments we used this concentration.

Finally, we acquired a 4D flow scan (TE/TR 8.1/4.5 msec; VENC 80 cm/sec; spatial resolution 0.5 × 0.5 × 0.5 mm; 10 cardiac phases) to analyze the relationship between flow suppression and flow velocity. The 4D flow MR scan was acquired with an acceleration factor of 5 in combination with a compressed sensing reconstruction strategy in order to speed up the scan time.[13]

3D TSE VWI Techniques

We acquired 3D TSE VWI scans with and without MSDE and DANTE preparation pulses, at an isotropic resolution of 0.7 mm. All VWI acquisitions used the same variable flip angle scheme and a field of view of 320 × 320 × 140 mm. The TRs were 700 msec for 3D TSE and MSDE-prepared VWI, and 1000 msec for the DANTE-prepared VWI. It is important to note that pump rates of 77 and 48 bpm were chosen to ensure VWI acquisition throughout the entire pulsatile cycle. Pump frequencies synchronized with VWI TRs had resulted in unreliable behavior of flow-suppressing performance in previous experiments (e.g., pump frequency of 1 Hz [60 bpm] with VWI repetition times of 1000 msec).

Analyses

A mask along the aneurysm wall was created to analyze near-wall signal intensities in VWI (Fig. 4). Additionally, a mask was created for a static agar region. Near-wall signal intensities were normalized to the mean agar intensity

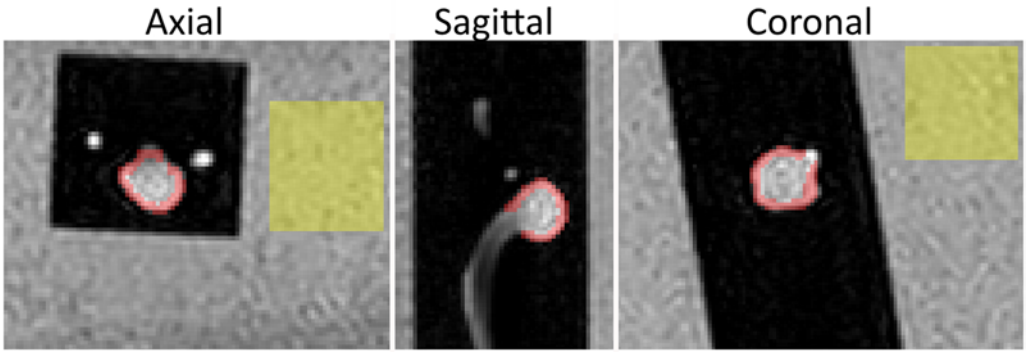

FIG. 4. Masks for signal intensity calculations. The intraluminal mask along the aneurysm wall is shown in *red*. The agar mask is shown in *yellow*. To calculate the relative intensity, signal intensities along the aneurysm wall were normalized to the average intensity of the masked agar tissue.

to make them comparable between VWI sequences. Box plots and histograms of normalized signal intensities were visually compared between pre- and postcontrast VWI, separately for each VWI technique and pump setting.

Results

Signals originating from slow flow along the aneurysm wall were observed for all VWI techniques and became more apparent after contrast enhancement, especially at lower pump rates (Fig. 5). Visual assessment of VWI suggested that preparation pulses improved flow suppression. Histograms and box plots of normalized signal intensities along the aneurysm wall demonstrated clear differences between VWI techniques (Fig. 6). After MSDE preparation, flow suppression improved. A larger effect on flow suppression improvement was observed for DANTE preparation. Near-wall signal intensities decreased by approxi-

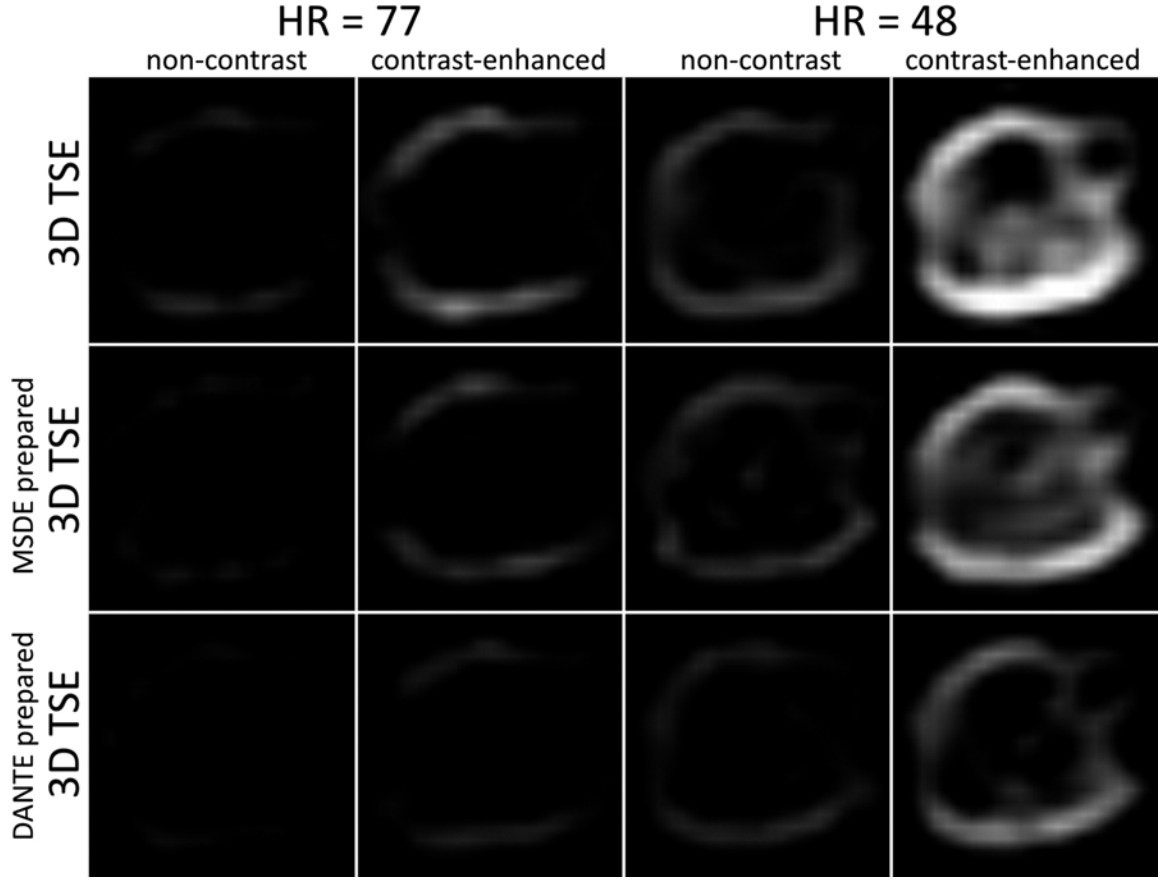

FIG. 5. VWI before and after contrast enhancement for different VWI techniques (rows) and inflow settings (columns). Visual assessment suggests that signal intensities are higher in contrast-enhanced groups and at a lower pump rate. HR = heart rate.

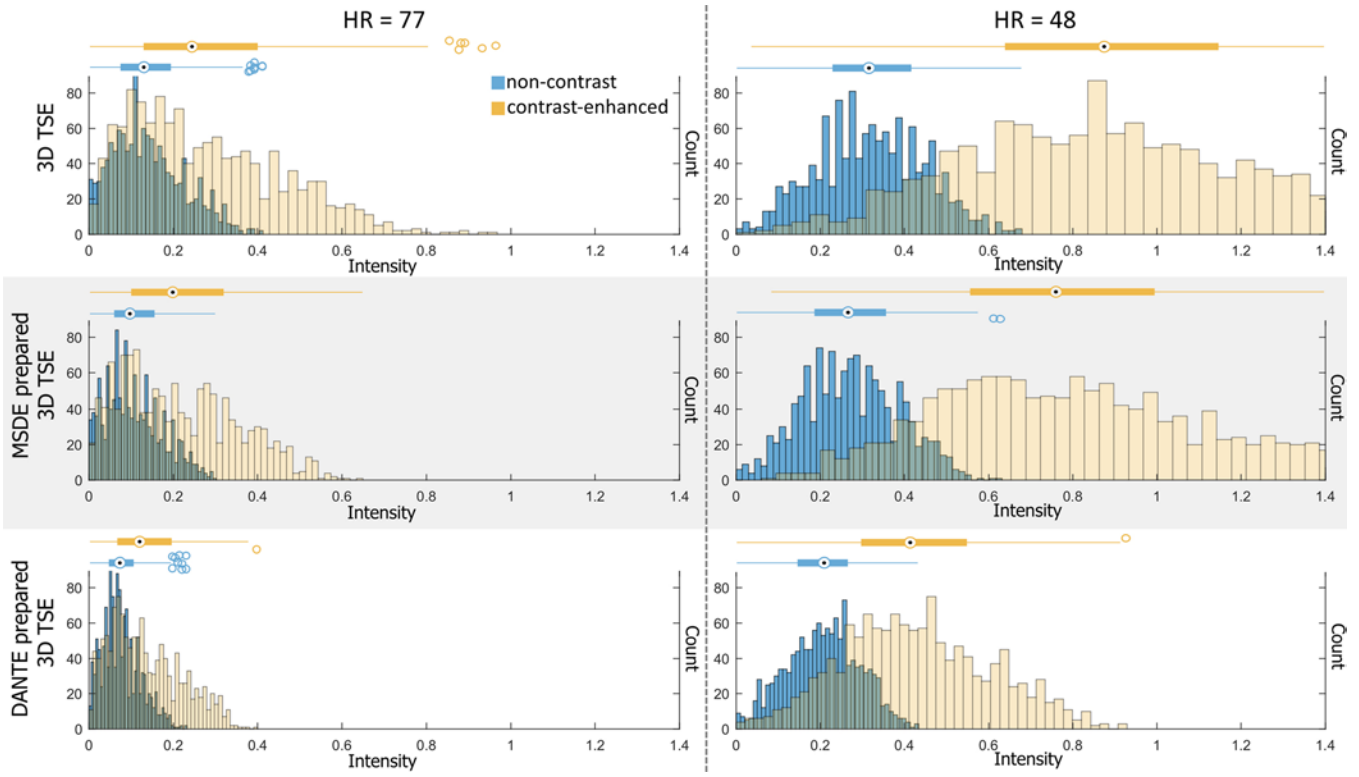

FIG. 6. Histograms and box plots (*blue* and *yellow horizontal bars*) of the near-wall intraluminal signal intensity, normalized to the surrounding agar intensity. Different VWI techniques are presented in each row, and each column represents a different inflow condition. The histograms are transparent; *gray vertical bars* show the overlap between VWI studies obtained with and without contrast.

mately 50% after DANTE preparation, compared to 3D TSE VWI alone. Figure 7 shows a comparison between contrast-enhanced 3D TSE VWI and 4D flow imaging for the same slice location. The region of high flow velocity clearly corresponds to the dark, suppressed region in VWI. This confirms the relationship between flow and suppression.

Discussion

In our phantom model, we observed wall-like MR signal along the aneurysm wall in VWI both with and without preparation pulses. After contrast agent administration, these signals became more apparent, especially at low pump rates. Signal originating from unsuppressed blood may easily be mistaken for aneurysm wall. Therefore, we underline the importance of careful interpretation of VWI. Preparation pulses, especially the DANTE technique, improved flow suppression.

Contribution of Slow Flow to Enhancement in VWI

To our knowledge, this is the first analysis of flow-related artifacts in VWI in a controlled phantom setup. However, the contribution of slow flow to aneurysm wall enhancement has been assessed in patients harboring unruptured intracranial aneurysms by comparing VWI with and without MSDE preparation pulses.[5] Wall enhancement was observed less often in MSDE-prepared VWI, suggesting wall-mimicking enhancement on conventional VWI without preparation pulses. Comparably, in our study we showed lower signal intensities along the wall for MSDE-prepared VWI, compared to VWI without a preparation pulse. Another study emphasized that slow-flow artifacts, which are most obvious in slow-flowing blood in veins, may result in misinterpretation of enhancement of surrounding arterial vessel walls.[8] Similarly, we observed slow-flow artifacts in slow-flowing blood in the aneurysm sac, which may easily be misinterpreted as aneurysm wall enhancement.

Traditional Risk Factors (Lesion Size and Shape) are Sensitive to Contribution of Slow Flow in VWI

Various studies have presented relationships between aneurysm wall enhancement and aneurysm instability, often neglecting the potential influence of slow flow on wall assessment. Aneurysm wall enhancement has been observed at irregular regions and daughter sacs of aneurysms.[16] Because slow and turbulent flow characteristics are expected in irregular aneurysm regions, flow suppression could have been hindered, resulting in wall-like enhancement. Similarly, several studies have shown a relationship between wall enhancement and aneurysm size.[1,9,10,20] However, larger aneurysms are most likely also to be associated with lower flow velocities, which reduces flow suppression performance. Furthermore, regions of low wall shear stress (WSS) have been related to wall enhancement.[19] Because

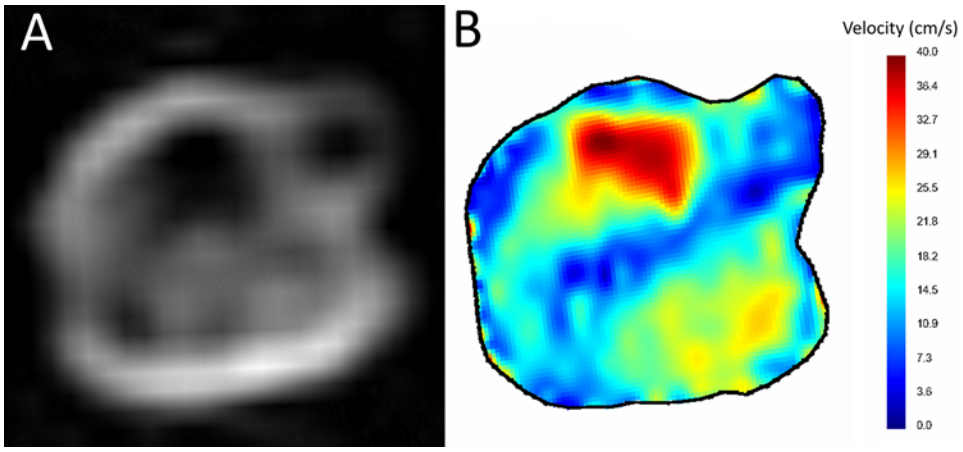

FIG. 7. A comparison between contrast-enhanced 3D TSE VWI at 48 bpm (**A**) and 4D flow imaging (**B**) at the same location at 60 bpm. The region of high flow velocity clearly corresponds to the *dark region* in VWI. This confirms the relationship between suppression and flow.

low WSS is related to lower velocities near the wall, insufficient suppression of slow flow in VWI could have contributed to wall enhancement. Putting it into perspective, slow flow contributes to low WSS, which has been suggested to be related to inflammation in the aneurysm wall.[15] Therefore, in enhanced unstable aneurysms, enhancement is most likely to be caused by a combination of slow flow and inflammation in the aneurysm wall.

Study Limitations

Our study has several limitations. We created pulsatile inflow conditions comparable to physiological MCA peak flow rates. However, we could not recreate physiological diastolic flow rates (approximately 1.5 ml/sec at late diastole) by using the MR-compatible pump. Instead, no flow was present in late diastole. This may have resulted in an overestimation of unsuppressed flow signal when compared to an in vivo situation. In addition, we modeled different flow velocities by using different pump rates with similar peak flows. In vivo, not only heart rate, but also stroke volume, hypertension, and other hemodynamic parameters may affect local flow velocities. However, our study indicates that in regions with slow flow, insufficient flow suppression mimics aneurysm wall enhancement. Another limitation is the rigid design of our phantom model, which does not allow pulsatile behavior along the wall. Arterial compliance probably results in higher blood flow velocities along the vessel wall compared to our phantom model. This may have resulted in a higher chance of false-positive enhancement. However, we believe that slow and recirculating flow characteristics are inherently related with intracranial aneurysms that—depending on aneurysm size and shape—may contribute to wall-mimicking enhancement. Finally, we used water instead of blood for our experiments. Water lacks the non-newtonian behavior of blood and, more importantly, it has a lower viscosity compared to blood. Lower flow velocities near the vessel wall can be expected in more viscous fluids. In theory, flow suppression would have been worse when using a higher-viscosity fluid in our phantom setup.

Conclusions

Insufficient slow-flow suppression mimics aneurysm wall enhancement in MR VWI. Therefore, vessel wall imaging should be carefully interpreted. Preparation pulses improve slow-flow suppression; therefore, we encourage further development and clinical implementation of these flow suppression techniques.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: all authors. Acquisition of data: Cornelissen, Leemans, Coolen, Peper. Analysis and interpretation of data: all authors. Drafting the article: Cornelissen. Critically revising the article: Leemans, Coolen, Peper, van den Berg, Marquering, Slump, Majoie.

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