Noncontrast dynamic MRA in intracranial arteriovenous malformation (AVM): comparison with time of flight (TOF) and digital subtraction angiography (DSA)

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Abstract

Digital subtraction angiography (DSA) remains the gold standard to diagnose intracranial arteriovenous malformations (AVMs) but is invasive. Existing magnetic resonance angiography (MRA) is suboptimal for assessing the hemodynamics of AVMs. The objective of this study was to evaluate the clinical utility of a novel noncontrast four-dimensional (4D) dynamic MRA (dMRA) in the evaluation of intracranial AVMs through comparison with DSA and time-of-flight (TOF) MRA. Nineteen patients (12 women, mean age 26.2±10.7 years) with intracranial AVMs were examined with 4D dMRA, TOF and DSA. Spetzler–Martin grading scale was evaluated using each of the above three methods independently by two raters. Diagnostic confidence scores for three components of AVMs (feeding artery, nidus and draining vein) were also rated. Kendall’s coefficient of concordance was calculated to evaluate the reliability between two raters within each modality (dMRA, TOF, TOF plus dMRA). The Wilcoxon signed-rank test was applied to compare the diagnostic confidence scores between each pair of the three modalities. dMRA was able to detect 16 out of 19 AVMs, and the ratings of AVM size and location matched those of DSA. The diagnostic confidence scores by dMRA were adequate for nidus (3.5/5), moderate for feeding arteries (2.5/5) and poor for draining veins (1.5/5). The hemodynamic information provided by dMRA improved diagnostic confidence scores by TOF MRA. As a completely noninvasive method, 4D dMRA offers hemodynamic information with a temporal resolution of 50–100 ms for the evaluation of AVMs and can complement existing methods such as DSA and TOF MRA.

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1. Introduction

Intracranial arteriovenous malformations (AVMs) are congenital vascular abnormalities characterized by direct arteriovenous shunts through a nidus of coiled and tortuous vascular connections without a normal intervening capillary bed. The principal presentation of AVM patients is hemorrhage which accounts for 2%-4% of overall hemorrhagic strokes [1], conferring significant morbidity and mortality. Detailed information about the architecture and hemodynamics of AVM is of great value with respect to adequate diagnosis and ensuing therapeutic approaches [2].

Digital subtraction angiography (DSA) remains the gold standard for the characterization and delineation of intracranial AVMs. However, as an invasive technique, it exposes both doctors and patients to the radiation of X-rays and carries risks related to puncture of femoral artery, catheter placement, contrast agents and experience of doctors [3]. Time-resolved contrast-enhanced magnetic resonance angiography (CE-MRA) is a promising technique in the assessment of both anatomic and hemodynamic information, but its temporal resolution is relatively
low (generally on the order of seconds), which might not be sufficient to capture the fast-flow hemodynamic information. Also, complications may occur with the application of gadolinium-based contrast agents such as nephrogenic systemic fibrosis when the glomerular filtration rate is lower than 30 ml/min [4]. Standard time-of-flight (TOF) MRA provides static vascular images with high spatial resolution; however, it cannot provide hemodynamic information. Recently, an unenhanced four-dimensional (4D) time-resolved dynamic MRA (dMRA) technique was introduced by combining arterial spin tagging with a multiphase true fast imaging with steady-state precession (TrueFISP) sequence [5,6]. In preliminary studies, this 4D dMRA technique was able to delineate the dynamic course of blood flow through an AVM with a temporal resolution of a few tens of milliseconds and a spatial resolution of a few cubic millimeters.

In this paper, we attempted to evaluate the clinical utility of the 4D dMRA technique in a cohort of AVM patients using Spetzler–Martin grading scale (size, eloquence of adjacent brain and pattern of venous drainage) [7] (Table 1), which has been traditionally used to estimate the risk of surgical intervention, as the reference. In addition, other factors that are important for the evaluation of AVMs or deemed as significant determinants of risks and outcomes such as the pattern of supplying artery and draining vein, AVM-related aneurysms, presence of arteriovenous fistula (AVF) and detailed hemodynamic information were evaluated [8–10]. These results were then compared with those of DSA and TOF MRA, respectively, to test whether the information derived from dMRA is consistent with the gold standard of DSA and whether dMRA will improve the existing diagnosis based on TOF MRA.

2. Materials and methods

2.1. Patients

This study was approved by the institutional review boards, and written informed consent was obtained from all patients. The general contraindications for MR examination were applied and defined as exclusion criteria.

Between July 2009 and November 2010, 19 patients (12 women, 7 men, mean age 26.2±10.7 years) with intracranial AVM scheduled for DSA examination were included in this prospective study. Among them, four patients experienced spontaneous intracranial hemorrhage (all occurred within 4 months before they were hospitalized in our hospital) and were treated conservatively in their local hospitals. One patient had gamma-knife treatment, and another underwent endovascular interventional treatment. The time interval between DSA and dynamic MRA was 1–68 days (15.4±20.6 days).

2.2. Conventional DSA

DSA was performed according to a standard protocol during routine clinical examination on a biplane angiography system (Advantx LCV+, GE Healthcare, UK). A 5-Fr diagnostic catheter was navigated into internal carotid and vertebral arteries, respectively, via the right femoral artery to acquire standard anteroposterior and lateral projections, each by manual delivery of 5–7 ml iodinated contrast agent ioxaglate injection per run (Visipaque, GE Healthcare, Ireland).

2.3. MR angiography

All imaging was performed on a 3-T MR imager (Tim Trio; Siemens, Erlangen, Germany) with a body coil as the transmitter and a 12-channel head array coil as the receiver. Conventional MR sequences included axial T1-weighted three-dimensional (3D) magnetization prepared rapid acquisition gradient-echo [repetition time (TR)/echo time (TE)=1760/3.1 ms, inversion time=950 ms, spatial resolution=1 mm×1 mm×1 mm], T2-weighted fast spin-echo (TR/TE=4000/87 ms, spatial resolution=0.43 mm×0.43 mm×1 mm×1 mm×1 mm, flip angle=25°) and TOF MRA (TR/TE=33/3.86 ms, spatial resolution=0.57 mm×0.57 mm×0.65 mm).

dMRA was implemented using flow-sensitive alternating inversion recovery (FAIR) [11] for spin tagging. Slice-selective (label) or nonselective (control) inversion recovery signals were continuously sampled by a 3D segmented multiphase TrueFISP sequence, and the difference of the two acquisitions provided 4D dMRA signals [6]. To minimize the effects of cardiac pulsation on dynamic MRA images, cardiac-gated dMRA was performed in 19 AVM patients. A slab of 64 slices was acquired (TR=2.94 ms, TE=TR/2, spatial resolution=1 mm×1 mm×1 mm, flip angle=25°). Depending on the cardiac cycle, 10–17 phases of dMRA images with a temporal resolution of 83 ms were acquired within approximately 6 min. After dynamic MR angiograms were obtained, maximum intensity projection (MIP) images were then generated for each phase along three directions which were displayed as a movie to visualize the dynamic flow patterns of AVM lesions [6].

2.4. Statistical analysis

One neuroradiologist (with 14 years’ experience) and one neurosurgeon (with 8 years’ experience) reviewed the cases independently. They were blinded to the information regarding the patients’ name and clinical history. The order of the 19 cases was randomized. First they graded AVMs

<table>
<thead>
<tr>
<th>Size of nidus</th>
<th>Eloquent</th>
<th>Venous drainage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 cm</td>
<td>1</td>
<td>Noneloquent 0</td>
</tr>
<tr>
<td>3–6 cm</td>
<td>2</td>
<td>Eloquent 1</td>
</tr>
<tr>
<td>&gt;6 cm</td>
<td>3</td>
<td>1鎌</td>
</tr>
</tbody>
</table>
according to Spetzler–Martin grading scale and evaluated other detailed information (the pattern of supplying artery and draining vein, AVM-related aneurysms and AVF). This step was carried out with dMRA only. Then they were asked to give diagnostic confidence scores according to the information gathered above for each component of an AVM (feeding artery, nidus and draining vein). One week later, they repeated the evaluation procedures with TOF MRA first and then with combined TOF and dMRA together. Another week later, they repeated the evaluation procedures again but with DSA only. During all evaluation procedures, conflicting readings were resolved by consensus of the two raters. The diagnostic confidence score was defined as follows: score 5, excellent imaging quality with clear detailed vascular architecture and hemodynamic information, with no artifacts and can be diagnosed definitely; score 4, good imaging quality with fine vascular architecture and hemodynamic information, with mild artifacts and relatively clear diagnosis can be drawn; score 3, ordinary imaging quality and detailed vascular architecture and hemodynamic information need to be distinguished with some efforts, with moderate artifacts and possible diagnosis can be obtained; score 2, poor imaging quality and bad vascular architecture and hemodynamic information, with sever artifacts but can be helpful to the diagnosis; score 1, cannot afford any help to diagnosis.

Kendall’s coefficient of concordance was calculated to evaluate the reliability between two readers within each modality (dMRA, TOF, TOF plus dMRA). A Kendall’s coefficient of concordance higher than 0.75 was considered to indicate excellent agreement. The Wilcoxon signed-rank test was applied to compare the diagnostic confidence scores between each pair of the three modalities for each component of an AVM, respectively. A two-tailed $P$ value of .05 or less indicated significant difference. All statistical analyses were performed with STATA 10.0 software (StataCorp, College Station, TX, USA).

3. Results

All the 19 AVMs demonstrated a typical appearance with one or more feeding arteries, an appreciable nidus and at least one readily identifiable draining vein entering venous sinuses, and no AVM-related aneurysm or AVF was found on DSA. Dynamic MRA was able to depict the entire dynamic blood circulation from arterial feeders to draining veins of cerebral AVM in accordance with DSA (Fig. 1, Supplemental Video 1). It failed to detect AVM lesions in three patients (patient nos. 1, 7, 12). In patient no. 1, severe artifact due to patient’s movement during examination led to poor image quality. In patient nos. 7 and 12, both dMRA and TOF MRA showed inabilities to detect intracranial AVMs with low blood flow which was manifested as lightly stained on DSA (Fig. 2).

3.1. Spetzler–Martin grading scale

Dynamic MRA provided a fine delineation with respect to the size and location but a poor depiction as to the detection of draining veins of AVM. TOF encountered similar problems as dMRA. Spetzler–Martin grading scale could be completed only in four patients (patient nos. 4, 9, 13, 14) on dMRA imaging and in six patients on TOF MRA (patient nos. 4, 8, 9, 14, 16, 18).

Dynamic MRA provided correct evaluation of the sizes and locations of all the 16 AVMs detected, and the scores based on Spetzler–Martin classification were in complete accordance with those evaluated by DSA (Table 2). In contrast, TOF provided correct evaluation of AVM sizes in 15 of the 18 AVM lesions detected and was inaccurate in 3 AVMs (patient nos. 7, 11, 18). All of the three patients had a history of spontaneous intracerebral hemorrhage, and the high signal intensity caused by methemoglobin completely obscured (no. 11) or disturbed (no. 18) AVM anatomy. As a result, the apparent size of AVM was enlarged (Fig. 3, Supplemental Video 2), while in another patient (no. 7), the signal due to methemoglobin was mistaken for AVM lesion (Fig. 2). Moreover, dMRA can visualize dynamic blood flow and thus can provide a better view of AVM size in late stages of the arterial filling phase (Fig. 4).

Improved diagnostic accuracy was achieved when dMRA and TOF MRA were combined. In 17 of the 19 patients (excluding no. 7), Spetzler–Martin grading scale of AVM size and location based on dMRA plus TOF completely matched that of DSA (Table 2).

3.2. Diagnostic confidence

Compared with DSA, dMRA detected 22 of all the 29 feeding arteries (75.8%) and 5 of all the 25 draining veins (20%) correctly in 19 patients. TOF MRA detected 26 of all the 29 feeding arteries (89.7%) and 7 of all the 25 (28%) draining veins. The two modalities combined together were able to detect 26 of all the 29 feeding arteries (89.7%) and 8 of all the 25 (32%) draining veins. Compared with TOF, dMRA has advantages in the observation of dynamic blood flow with a high temporal resolution (83 ms per frame). In three patients (nos. 1, 5, 17), occlusion of unilateral transverse sinus can be observed via dMRA (Fig. 5).

The average scores of diagnostic confidence of the 19 patients for feeding artery, nidus and draining vein by means of dMRA, TOF and dMRA plus TOF, respectively, are displayed in Table 3. The diagnostic confidence scores were relatively high and adequate for diagnosis with respect to the depiction of nidus, moderate when describing feeding arteries and insufficient to make a correct diagnosis for draining veins in all the three modalities. Compared with dMRA, TOF provided a better result in the scoring of feeding arteries with statistical significance ($P$=.002). TOF and dMRA were not statistically different in the scoring for nidus and draining veins ($P>.05$). When dMRA was
combined with TOF, the obtained diagnostic confidence scores of feeding arteries \((P = .0002)\), nidus \((P = .0004)\) and draining veins \((P = .005)\) were significantly improved compared to those from dMRA alone. The confidence scores obtained from dMRA plus TOF of the nidus \((P = .009)\) and draining veins \((P = .046)\) were also significantly improved compared to those based on TOF MRA alone. The confidence score from dMRA plus TOF of feeding arteries did not change significantly compared to those based on TOF MRA \((P > .05)\).

4. Discussion

Spetzler–Martin grading scale has been traditionally used to estimate the risk of surgical intervention for intracranial...
AVM and has been validated by its correlation with outcomes for surgically treated patients. All AVMs fall into one of six grades, and the higher the grade is, the poorer the outcome for operative treatment. Many risk factors have been studied to predict hemorrhage of intracranial AVM. Some research showed that patients with small (≤3 cm) AVMs presented more frequently with hemorrhage than did patients with larger AVMs (>3 cm) [12–14]. Previous rupture of intracranial AVM has been confirmed to be an independent predictor of subsequent hemorrhage [1,15]. The yearly risk of death at the first bleeding is about 10% and will increase with each bleeding [16]. So it is of great importance to correctly evaluate AVM in patients with hemorrhage history.

In this pilot study, we have successfully applied unenhanced 4D dMRA for the clinical evaluation and diagnosis of AVM patients before operations. As a newly emerging technology, 4D dMRA possesses several advantages for dynamic flow imaging such as inherent flow compensation [17], and relatively high contrast-to-noise ratio and signal-to-noise ratio [6]. The temporal resolution (83 ms per frame) is much higher than that generally acquired by CE-MRA [18,19]. The relatively short acquisition time (6–7 min) makes it feasible to be implemented in routine clinical care. This modality has recently been tested clinically in the evaluation of intracranial collateral flow in patients with steno-occlusive diseases of brain-supplying arteries [20]. During the preparation of this manuscript, a similar study was conducted in 15 AVM patients, and the results showed that the consistency between non-contrast-enhanced dMRA and DSA was excellent for the arterial feeders, good for the nidus size and moderate for the venous drainage. Our data are consistent with the reported findings. Furthermore, we performed comparisons between dMRA and TOF MRA.

### Table 2

Spetzler–Martin grading score from four modalities

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>dMRA</th>
<th>TOF</th>
<th>dMRA plus TOF</th>
<th>DSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>×</td>
<td>S2E1</td>
<td>S2E1</td>
<td>S2E1V0</td>
</tr>
<tr>
<td>2</td>
<td>S2E0</td>
<td>S2E0</td>
<td>S2E0</td>
<td>S2E0V0</td>
</tr>
<tr>
<td>3</td>
<td>S1E1</td>
<td>S1E1</td>
<td>S1E1</td>
<td>S1E1V0</td>
</tr>
<tr>
<td>4</td>
<td>S2E1V0</td>
<td>S2E1V0</td>
<td>S2E1V0</td>
<td>S2E1V0</td>
</tr>
<tr>
<td>5</td>
<td>S1E1</td>
<td>S1E1</td>
<td>S1E1</td>
<td>S1E1V0</td>
</tr>
<tr>
<td>6</td>
<td>S2E1</td>
<td>S2E1</td>
<td>S2E1</td>
<td>S2E1V0</td>
</tr>
<tr>
<td>7</td>
<td>×</td>
<td>S1E1</td>
<td>S1E1</td>
<td>S1E1V0</td>
</tr>
<tr>
<td>8</td>
<td>S2E1</td>
<td>S2E1V0</td>
<td>S2E1V0</td>
<td>S2E1V0</td>
</tr>
<tr>
<td>9</td>
<td>S2E1V0</td>
<td>S2E1V0</td>
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<td>S2E1V0</td>
</tr>
<tr>
<td>10</td>
<td>S2E0</td>
<td>S2E0</td>
<td>S2E0</td>
<td>S2E0V0</td>
</tr>
<tr>
<td>11</td>
<td>S1E1</td>
<td>S3E1</td>
<td>S1E1</td>
<td>S1E1V0</td>
</tr>
<tr>
<td>12</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>S1E0V0</td>
</tr>
<tr>
<td>13</td>
<td>S2E1V0</td>
<td>S2E1</td>
<td>S2E1V0</td>
<td>S2E1V0</td>
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<tr>
<td>14</td>
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<td>S2E1V0</td>
<td>S2E1V0</td>
</tr>
<tr>
<td>15</td>
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<td>S2E0</td>
<td>S2E0</td>
<td>S2E0V0</td>
</tr>
<tr>
<td>16</td>
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<td>S3E1V0</td>
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</tr>
<tr>
<td>17</td>
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<td>S2E1</td>
<td>S2E1</td>
<td>S2E1V1</td>
</tr>
<tr>
<td>18</td>
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<td>S2E1V0</td>
<td>S1E1V0</td>
<td>S1E1V0</td>
</tr>
<tr>
<td>19</td>
<td>S1E1</td>
<td>S1E1</td>
<td>S1E1</td>
<td>S1E1V0</td>
</tr>
</tbody>
</table>

Note: S=size of cerebral AVM nidus; E=eloquence of adjacent brain; V=venous drainage pattern. Absence of V (in the form of SE) means that this method fails to detect venous drainage pattern. “×” means failure to detect intracranial AVM lesion.

Although TOF grading score was consistent with DSA, high intensity on TOF was caused by methemoglobin instead of AVM.
4.1. dMRA vs. DSA

Compared with DSA, dMRA is a totally noninvasive examination with a faster acquisition time which avoids sophisticated surgical procedures, the injection of iodinated contrast agent and the exposure to ionizing radiation. Also, this technique does not require hospitalization and costs less. Furthermore, it does not increase the emotional stress of patients.

In the 16 positive results detected by dMRA, the demarcation of AVMs was well defined, which allowed satisfactory results for both location and size judgments. All the scoring for size measurement and whether it occurs in eloquent areas according to Spetzler–Martin grading scale were completely in accordance with those from DSA. In this respect, dMRA is comparable to DSA. Furthermore, dMRA can provide anatomic information, and clinical neurosurgeons are more familiar with its presentation form (axial, sagittal and coronary presentation). Dynamic MRA showed poor ability to detect draining veins mainly due to the short coverage of time window which was insufficient to capture entire venous filling phrase. In the current implementation of dMRA, a tradeoff had to be made to balance the coverage of time window and spatial resolution in the slice direction. In the 16 positive patients, dMRA detected 22 of 26 feeding arteries (84.6%) correctly and did not miss any dominating feeding arteries which are more valuable to surgical strategy. However, it was demonstrated to be insensitive to tenuous or tiny feeding arteries.

The use of FAIR for spin tagging can cause contamination of labeled venous signals. In this study, six AVMs demonstrated the abnormal filling of superior sagittal sinus within artery filling phase before the filling of vascular nidus which indicated a fast blood velocity through AVMs, and the
existence of arteriovenous fistula was suspected. But this phenomenon was denied by DSA, and no early fillings of superior sagittal sinus were detected.

4.2. dMRA vs. TOF

Compared with TOF, dMRA is a dynamic technique with a high temporal resolution allowing the observation of the passage of labeled blood from feeding arteries through abnormal vascular nidus to draining veins and then into venous sinuses. Thus, it is more vivid and has the potential to separate feeding arteries from the draining veins and present more detailed information such as the estimation of blood flow velocity, degree of shunt, detection of AVF and so on. In this study, we observed the occlusion of unilateral transverse sinus in three patients via the dynamic images which were confirmed by DSA but were invisible on TOF MRA.

As for Spetzler–Martin classification, dMRA was superior for size measurement in patients who had a history of intracranial hemorrhage and showed the ability to detect small AVMs with a minimum size of 8 mm in this study. Dynamic MRA images were obtained by complex subtractions of selective and nonselective inversion-recovery TrueFISP images which offered a better suppression of background signal intensity arising from methemoglobin. TOF did poorly in this aspect and was susceptible to the high signal intensity of methemoglobin which might obscure or disturb AVM anatomy, or might be mistaken for components of AVM [22]. On the other hand, TOF provides static vascular imaging, and the overlapping of vessels may disturb the observation of an AVM. In contrast, we can achieve a good view of AVM entity via dMRA during the late stages of arterial filling phase or capillary phase. Both dMRA and TOF provided a fine and accurate depiction of the location but demonstrated poor ability in identifying the draining veins.

As for diagnostic confidence scoring, TOF had relatively higher average scores than dMRA for each component of AVM. The reason may be that the higher spatial resolution of TOF facilitates the observation of static anatomical structures. However, in some patients, dMRA can provide additional temporal information and are more reliable in patients experiencing cerebral hemorrhage. More importantly, improved diagnostic confidence was achieved with combination of dMRA and TOF MRA, which provided high temporal and spatial resolution for 4D vascular imaging, respectively. Since both dMRA and TOF are noninvasive procedures, the only cost for their combined use in clinical routine care is an additional scan time of several minutes plus the time for radiologists to view the 4D images.

4.3. Disadvantage of dMRA

Despite its advantages, dMRA encounters challenges for the evaluation of intracranial AVMs as demonstrated by this pilot study. Firstly, it is insensitive to intracranial AVMs with low blood flow. This caused the failure of detection of AVMs in two patients and low diagnostic confidence in another two patients. Secondly, the time coverage is relatively short (1 s or so in cardiac-gated dMRA) and is not long enough to capture the entire dynamic course of blood flow through AVM lesions, which leads to a poor detection of draining veins that is of great importance for risk evaluation. Finally, contamination of venous blood would mislead observers to give a wrong judgment. Some of these technical limitations are currently being addressed through implementation of fast
image acquisition schemes such as undersampled radial acquisition, parallel imaging, compressed sensing, etc. [23], which allow prolonged time coverage without sacrificing spatial resolution in 4D dMRA. Another potential improvement of dMRA, which also eliminates venous contamination, is to apply more efficient spin labeling schemes including the newly introduced pseudocontinuous ASL [24] as well as vessel selective labeling [25,26] for observing the dynamic inflowing pattern of a particular artery of interest. The present study was conducted at 3 T, which should provide advantages for spin-labeling-based methods. However, a recent study reported that the performance of noncontrast 4D dMRA was superior at 1.5 T compared to 3 T, probably due to reduced susceptibility and saturation effects of SSFP at 1.5 T [27]. In future clinical studies, the optimal field strength and imaging parameters for noncontrast dMRA need to be evaluated.

5. Conclusion

As a newly emerging and promising technique, noncontrast unenhanced dMRA can be easily implemented in
clinical routines due to its noninvasive feature and relatively fast acquisition time. In this pilot study performed on 19 AVM patients, dMRA was capable in depiction of the size and location of AVM, moderate in description of feeding arteries and poor in detection of draining veins. Most information it provided was in accordance with DSA. Although it cannot replace either DSA or TOF for clinical diagnosis of AVMs according to the results of this study, it can provide complementary temporal information to TOF and thus enhance our diagnostic confidence. In the future, further development should be done to address its shortcomings and challenges.

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