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ABSTRACT

BACKGROUND AND PURPOSE: Brain AVMs represent the main etiology of pediatric intracranial hemorrhage. Noninvasive imaging techniques to monitor the treatment effect of brain AVMs remain an unmet need. In a large cohort of pediatric ruptured brain AVMs, we aimed to investigate the role of arterial spin-labeling for the longitudinal follow-up during treatment and after complete obliteration by analyzing CBF variations across treatment sessions.

MATERIALS AND METHODS: Consecutive patients with ruptured brain AVMs referred to a pediatric quaternary care center were prospectively included in a registry that was retrospectively queried for children treated between 2011 and 2019 with unimodal or multimodal treatment (surgery, radiosurgery, embolization). We included children who underwent an arterial spin-labeling sequence before and after treatment and a follow-up DSA. CBF variations were analyzed in univariable analyses.

RESULTS: Fifty-nine children with 105 distinct treatment sessions were included. The median CBF variation after treatment was -43 mL/100 mg/min (interquartile range, -102 – 5.5), significantly lower after complete nidus surgical resection. Following radiosurgery, patients who were healed on the last DSA follow-up demonstrated a greater CBF decrease on intercurrent MR imaging, compared with patients with a persisting shunt at last follow-up (mean, -62 [SD, 61] mL/100 mg/min versus -17 [SD, 40.1] mL/100 mg/min; $P = .02$). In children with obliterated AVMs, recurrences occurred in 12% and resulted in a constant increase in CBF (mean, $+89$ [SD, 77] mL/100 mg/min).

CONCLUSIONS: Our results contribute data on the role of noninvasive arterial spin-labeling monitoring of the response to treatment or follow-up after obliteration of pediatric AVMs. Future research may help to better delineate how arterial spin-labeling can assist in decisions regarding the optimal timing for DSA.

ABBREVIATIONS: ASL = arterial spin-labeling; EVT = endovascular treatment; IQR = interquartile range; SRS = stereotactic radiosurgery

Pediatric intracerebral hemorrhage accounts for half of strokes in children^{1–3} and has severe long-term medical and psychosocial consequences.⁴ In children, brain AVMs represent the main underlying risk factor for hemorrhage, being responsible for up to

80% of nontraumatic hemorrhages.^{1,3} Treatment strategy includes surgical excision, serial endovascular treatment (EVT), and stereotactic radiosurgery (SRS), alone or in combination, according to the AVM size and location. After the initial work-up and treatment of a ruptured AVM, invasive DSA is the criterion standard to tailor the adequate subsequent therapeutic strategy^{5,6} or to confirm the complete obliteration of the AVM. Nevertheless, repeat DSA exposes children to the long-term risks of ionizing radiation, injection of an exogenous contrast agent, multiple exposures to general anesthesia, and neurologic adverse events. Hence, in children with ruptured AVMs, evaluating noninvasive imaging techniques for the mid and long-term intermediate follow-up and treatment

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planning is an important purpose. In this context, MR imaging possibly represents the best noninvasive technique, and advanced techniques such as arterial spin-labeling (ASL) sequences have shown their role in detecting increased CBF in patients with AVMs⁶ and are useful tools in adults for the follow-up of AVMs after embolization⁷ or SRS.⁸⁻¹¹ Furthermore, accumulating evidence indicates that AVMs in children are more likely to re-appear after DSA-proved complete obliteration,^{12,13} reinforcing the need for prolonged follow-up and the drawbacks of invasive imaging in the setting of a healed shunt. A preliminary analysis from our group¹⁴ evaluated the CBF, computed using ASL after treatment in 21 patients (yet only including 9 patients who had undergone ASL both before and after therapeutic procedures), and demonstrated its potential role in the noninvasive follow-up of AVMs in patients under treatment or after treatment.

In a large cohort of children with an initially ruptured AVM, we aimed to investigate the role of ASL for the longitudinal follow-up of patients under treatment and after complete obliteration by analyzing CBF variations on pseudocontinuous ASL across treatment sessions.

MATERIALS AND METHODS

Study Design and Patient Selection

Consecutive patients referred to our institution, a pediatric quaternary care center and coordinating center for the French Pediatric Stroke Network, were prospectively enrolled in a registry initiated in 2008. The registry has been described elsewhere in detail.⁴ For the purpose of this analysis, the sample was restricted to children (1 month to 18 years of age) meeting the following criteria: 1) ruptured brain AVMs; 2) between January 2011 (date of ASL implementation at our site) and October 2019; 3) with unimodal or multimodal AVM treatment (surgery, SRS, embolization); and 4) an ASL sequence before and after treatment and intercurrent DSA, performed within 24 hours of the ASL sequence. Patients were excluded for the following reasons: 1) no ASL follow-up; 2) no DSA follow-up; 3) a ruptured AVM without treatment; and 4) lost to follow-up.

Imaging Acquisition

MR Imaging Procedure. MR imaging was performed for each patient with a Signa HDxt 1.5T system (GE Healthcare) and a 12-channel head-neck-spine coil. The MR imaging investigation included standard pulse sequences according to local AVM protocol: 3D T1WI, 4D-MRA, gadolinium-enhanced 3D T1WI, T2*WI, DWI, TOF-MRA of the circle of Willis, and unenhanced perfusion imaging with a 3D pseudocontinuous ASL sequence. Acquisition parameters for the ASL pulse sequence were unchanged since the beginning of the protocol:¹⁴ TR/TE, 4428/10.5 ms; postlabeling delay, 1025 ms; label duration, 1500 ms; 80 axial partitions; FOV, 240 × 240 × 4 mm; acquisition matrix, 8 spiral arms in each 3D partition with 512 points per arm; flip angle, 155°; acquisition time, 4 minutes 17 seconds.

Paired DSA and ASL. At our institution, follow-up DSAs are performed 3 years after SRS or after the last treatment to document AVM obliteration, 3 and 5 years thereafter, and at 18 years of age, whichever comes last. DSAs were performed with the patient

under general anesthesia in a dedicated neuroangiography suite. A brain MR imaging including an ASL sequence was performed systematically the day before DSA.

Imaging Analysis

DSA Analysis. Two readers (15 [O.N.] and 7 [G.B.] years of experience) evaluated DSA during a single joint reading session. A residual AVM was defined as the early opacification of a cerebral vein, visible in the vicinity of nidus location, during the arterial phase of angiographic runs.

MR Imaging and ASL Analysis. Image analysis was performed using a PACS, independently, by 2 readers (6 [J.F.H.] and 5 [B.K.] years of experience). Readers were blinded to clinical and follow-up data and reported patient and AVMs characteristics. The CBF map was automatically generated using the 3D-ASL application of the Advantage Windows Workstation Functool (GE Healthcare) postprocessing software. For qualitative analysis, the color scale was set to rainbow with the warmer color representing the highest CBF.

Criteria for the presence of an AVM on MR images were defined with the visualization of an early venous filling at the arterial phase (4D-MRA), enlarged and dilated serpiginous vessels (TOF-MRA, postgadolinium 3D-T1), and/or direct visualization of the fistulous point/nidus (TOF-MRA)¹⁵ and, for ASL, the presence of an intracranial venous hypersignal within the dural sinuses or cortical veins and a focal intravascular warm color ("hot spot") on a CBF map.

The quantitative analysis of ASL was staged as follows:

1. Visual inspection of the ASL-derived CBF maps and identification of the most densely perfused areas of the lesion, if present.
2. 2D ROI placement using a calibrated round 20-mm² ROI on the region where the CBF was visually of the highest value corresponding to the AVM nidus or draining vein. Inside each ROI, the nidus CBF (CBF_{nidus}) mean values were automatically calculated by the software. We analyzed the mean values of the 2 readers for each variable. For each patient, the ROI was placed in the exact same hot spot localization as in the MRIs performed before and after each treatment.
3. The relative lesion CBF, corresponding to the ratio of CBF_{nidus}/CBF_{cortex}, was obtained by normalizing CBF to a 20-mm² ROI in the contralateral normal-appearing cortical gray matter (CBF_{cortex}) in the cerebellum for posterior fossa AVMs and in the frontal and parietal lobes for supratentorial AVMs. Gray matter was chosen as a reference because it has a higher SNR.

If a difference of >10 mL/100 mg/min was realized between the 2 readers, a consensus was reached on CBF maps and other MR imaging sequences to best position the ROIs. In case of negative ASL findings following treatment, the nidus ROI was placed at the exact same localization as the presurgical ASL ROI after manual coregistration of MR imaging sequences.

Statistical Analysis

Baseline characteristics were explored using descriptive statistics as appropriate per variable makeup and are displayed as absolute number (percentage) or mean (SD) or median (interquartile

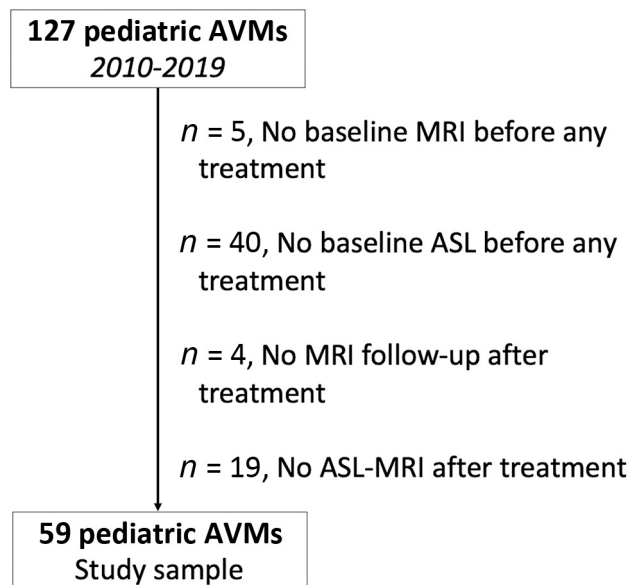


FIG 1. Flow chart of patient selection.

range [IQR], eg, 25th–75th quantiles). Univariable comparisons were performed using appropriate tests per variable makeup, distribution, and central tendency. All analyses were performed using JMP, Version Pro 14 (SAS Institute; 1989–2019), with $P < .05$ as a threshold for statistical significance.

RESULTS

Patients and AVM Characteristics

A total of 127 children were prospectively enrolled after 2011 in the database. After the application of study-specific inclusion and exclusion criteria, 59 patients were analyzed, and 68 patients were excluded. The flow chart in Fig 1 details patient selection. In included patients, AVMs were more frequently superficially located (57.4% versus 29.3%, $P = .02$). There was no difference between included and excluded patients in age at presentation (mean, 9.8 [SD, 3.7] versus 9.8 [SD, 3.8] years), clinical outcomes ($P = .36$), AVM location (supratentorial, 90% versus 83%, $P = .23$), and AVM grades ($P = .12$).

The 59 included patients benefited from 105 distinct treatment sessions with pre- and posttreatment MR imaging including ASL. The initial treatment was partial EVT, SRS, and partial and exhaustive microsurgery for, respectively, 38 (64.4%), 12 (20.3%), 3 (5.1%), and 6 (10.2%) children. Study sample baseline characteristics as well as treatments are detailed in the Table.

On baseline MR imaging performed before any treatment, findings of the visual inspection of the ASL-derived CBF map were considered positive in 56 patients (94.9%). The mean CBF_{nidus} was 192.1 (SD, 106) mL/100 mg/min with a mean ratio of lesion/cortex CBF of 2.2 (SD, 1.2).

AVM Follow-up of Patients under Treatment

General Considerations. We observed high interreader agreement for CBF measurement, using the Fleiss κ analysis ($\kappa = 0.92$; 95% CI, 0.8–1.0; $P < .0001$). The median CBF variation after treatment was -43 mL/100 mg/min (IQR, -102 – 5.5 mL/100 mg/min). There

Patient characteristics^a

Characteristics	
Clinical presentation	
Male sex (%)	28 (47.5%)
Age (median) (IQR) (yr)	10.1 (7.2–13.0)
Headaches	50 (84.7%)
Seizures	15 (25.4%)
Emesis	37 (62.7%)
Focal deficit	22 (37.3%)
GCS (median) (IQR)	14 (3–15)
ICH characteristics	
Supratentorial location	41 (69.5%)
ICH volume (median) (IQR) (mL)	10.9 (0.1–58)
ICH/TBV (median) (IQR) (%)	1.2 (0.8–5.6)
IVH	8 (13.6%)
Treatment characteristics	
Total No. of treatments	105
Patients treated with unimodal treatment	38 (64.4%)
Patients treated with multimodal treatment	21 (35.6%)
No. of treatment sessions (median) (IQR)	1 (1–6)
EVT	58 (55.2%)
EVT (No. of sessions) (median) (IQR)	1.5 (1–5)
SRS	26 (24.8%)
Partial surgery	6 (5.7%)
Complete surgery	15 (14.3%)
AVM characteristics	
Brain AVM	59 (100%)
SM grade 1–2	38 (64.4%)
SM grade 3	14 (23.7%)
SM grade 4–5	7 (11.9%)
Supratentorial	49 (83%)
Deep	31 (52.5%)
Eloquent area	33 (55.9%)
Nidus size (median) (IQR) (mm)	22 (9–60)
Compact nidus	38 (64.4%)
Aneurysm (arterial/venous)	25 (42.4%)
Any deep venous drainage	30 (50.8%)

Note:—GCS, indicates Glasgow Coma Scale; ICH, intracerebral hemorrhage; TBV, total brain volume; IVH, intraventricular hemorrhage; SM, Spetzler-Martin.

^a Variables are displayed as No. (%) or median (25th to 75th quantiles).

was a higher decrease in CBF after exhaustive nidal microsurgery ($n = 13$; median, -98 mL/100 mg/min [IQR, -161 to -50]) than after EVT, SRS, or partial microsurgery ($P = .002$). There was no significant difference in CBF variations after EVT versus SRS, SRS versus partial microsurgery, or EVT versus partial microsurgery (all $P > .05$) (see Fig 2 for details). The median time interval between MR imaging examinations was 10 months (IQR, 4–20 months).

CBF Variation after SRS. Twenty-seven patients were treated with SRS, and an ASL sequence was performed before and after treatment at each SRS session. The median interval time delay between sessions of MR imaging was 26 months (IQR, 12–39.5 months). Among these patients, DSA-proved complete obliteration at last follow-up was found in 14 patients (51.9%), whereas 13 patients were still under surveillance. The mean variation in CBF values on interval MRIs was -62 (SD, 61) mL/100 mg/min in eventually healed patients, whereas it was -17 (SD, 40.1) mL/100 mg/min in patients with incomplete obliteration at last follow-up ($P = .02$). In 8 of the 27 patients treated with SRS, CBF did not decrease ($\Delta > 0$), and only 2/8 (25%) of these patients' AVMs were obliterated at the latest follow-up.

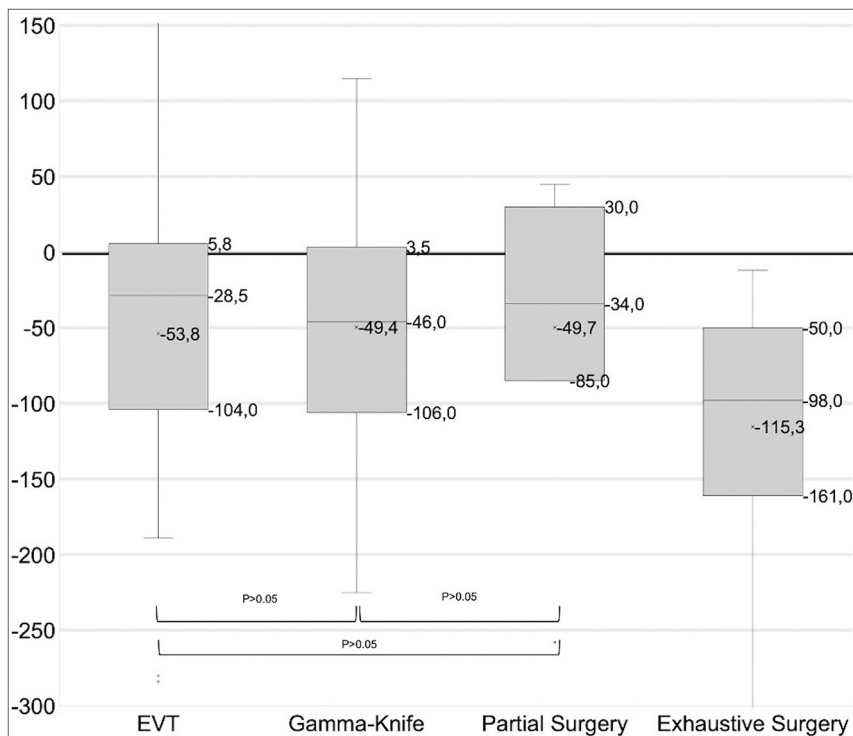


FIG 2. Boxplots of ASL variations by treatment technique per time interval.

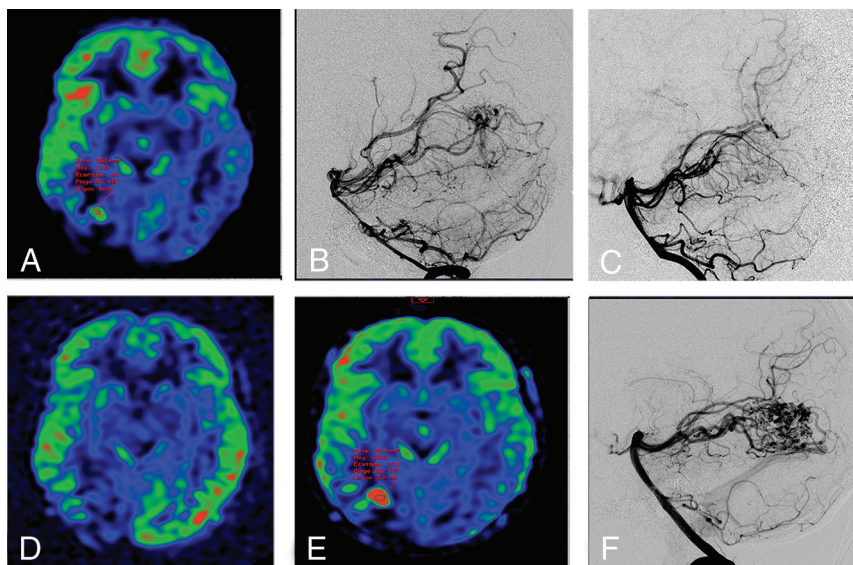


FIG 3. Example of a right occipital ruptured AVM confirmed with ASL (A) and DSA (B), completely treated with embolization 15 days after the initial diagnosis (C) and without a CBF increase, with ASL performed 4 months after the initial diagnosis (D). The 4-year ASL control revealed a focal ASL-derived CBF increase (E) suspicious for recurrence, confirmed with DSA (F).

After SRS, the mean CBF Δ for the healed children at 3 years versus the nonhealed at 3 years was, respectively, -68.3 (SD, 61.0) ($n = 4$) versus -14.5 (SD, 17.7) ($n = 2$) at 1 year after SRS ($n = 6$), and, respectively, -105.8 (SD, 66.3) versus 65.7 (SD, 150.3) at 2 years after SRS ($n = 19$). Thus, 1 year after SRS, a decrease in

CBF of $> 50 \text{ mL}/100 \text{ mg}/\text{min}$ was associated with a 3-fold increase in the rate of eventual obliteration after 3 years.

Follow-up after Complete Obliteration.

Among 34 patients achieving DSA-proved complete obliteration during follow-up, 4 (11.8%) children presented with a DSA recurrence at a mean delay of 21.8 [SD, 22.2] months. At the time of recurrence, the CBF increased in all patients by a mean of 89 (SD, 77) $\text{mL}/100 \text{ mg}/\text{min}$, corresponding to relative CBF lesion increases of a mean of 311% (SD, 147%). See Fig 3 for an example of recurrence after treatment.

DISCUSSION

We present robust data on the role of ASL in the noninvasive follow-up of ruptured pediatric AVMs during and after treatment. Our analysis notably shows that ASL-CBF increased in all patients with DSA recurrences, with direct clinical applications in children followed up after AVM obliteration. Furthermore, we showed that 1 year after SRS, a decrease in CBF of $> 50 \text{ mL}/100 \text{ mg}/\text{min}$ was associated with a 3-fold increase in the rate of eventual obliteration after 3 years. In our sample, patients with eventually healed AVMs after SRS had a mean CBF decrease of $-62 \text{ mL}/100 \text{ mg}/\text{min}$ when it was $-17 \text{ mL}/100 \text{ mg}/\text{min}$ in patients with incomplete obliteration at 3 years.

These results add to the evidence of the role of noninvasive imaging in objectively delineating treatment effect in pediatric AVMs, provide additional evidence justifying intermediate MR imaging follow-up of children with obliterated AVMs, and pave the way for noninvasive biomarkers of anticipated treatment effect, especially after SRS. An additional supporting argument was the high interreader agreement for CBF measurement, suggesting the reproducibility of our findings, at least internally.

Several adult studies reported a role for ASL in AVM follow-up after treatment. Suazo et al⁷ reported a fair agreement between ASL and DSA for the

assessment of shunt reduction achieved by embolization for 8 AVMs. Other studies focusing on SRS-treated AVMs reported a promising role for ASL: first, to show and quantify differences in AVM nidus flow ratios and the associated steal phenomena between treated and untreated groups;¹⁶ and second, to detect

incomplete-versus-complete AVM obliteration.⁸⁻¹¹ Altogether, these results contribute to determining the important role of ASL in AVM follow-up for patients under treatment or after obliteration, to minimize the use of DSA in the vulnerable sample of children with ruptured AVMs.

Pediatric AVMs have been shown to be dynamic lesions with vascular changes and higher rates of recurrence after complete obliteration, compared with adults.^{12,13} In addition, the susceptibility effects of the liquid embolic agents on perfusion imaging may hinder the quantitative perfusion measurements,¹⁷ justifying the need for our analysis in the subgroup of ruptured pediatric AVMs. This analysis complements a preliminary work from our group,¹⁴ in which 3 ruptured pediatric AVMs followed up after embolization alone showed a reduction in both nidus size and ASL-derived CBF values as well as 5 ruptured pediatric AVMs followed up after SRS, in which a reduction in the nidus size was observed, despite persistent elevated CBF_{nidus} values.

Despite these prior data, noninvasive AVM follow-up is an unmet need. Studies have evaluated 4D-MRA for AVM follow-up, but there are many practical drawbacks to the use of IV contrast in pediatric patients, including the need for IV access; increased scan time; children's fatigue, anxiety, and motion; and exposure to possible adverse effects of the contrast agent.¹⁸⁻²³ Conversely, ASL sequences allow quantitative mapping of CBF, without contrast injection,²⁴ and are known to be relevant in detecting the presence of arteriovenous shunts by demonstrating high signal in the nidus as well as arterialized venous structures.^{14,25-27}

In line with previous studies,^{7-11,16,28} we showed that most patients had decreased CBF after treatment with SRS or embolization, yet some lesions demonstrated no CBF decrease despite interval treatment. This finding supports the concept of dynamic AVM lesions in children, considered as an evolving vasculopathy rather than a simple amorphous vascular connection, with interval increasing arterial feeding and/or shunt acceleration. It appears, therefore, that AVMs have a remodeling potential that explains the reported cases of spontaneous growth^{29,30} as well as spontaneous regression.³¹⁻³³ Therefore, pretreatment ASL allows a radiation- and injection-free tool for treatment planning.

As previously reported, the AVM recurrence rate is higher for pediatric AVMs than for those in adults.^{12,13} In our cohort, 4 (11.8%) children presented with an angiographic recurrence with a CBF increase in all patients, by a mean of 89 (SD, 77) mL/100 mg/min. To our knowledge, we report the first preliminary data on ASL-CBF increase for the diagnosis of recurrent AVMs. We acknowledge, nonetheless, that our sample provides a limited number of recurrent AVMs and that this finding should be further supported by a larger study.

Note that at our institution, a pediatric quaternary care center and coordinating center for the French Pediatric Stroke Network, a DSA is performed in the initial AVM imaging assessment for angioarchitectural characterization and appropriate treatment. Following treatment, DSAs are performed 3 years after SRS or after the last treatment to document AVM obliteration, 3 and 5 years thereafter, and at 18 years of age, whichever comes last. Accordingly, DSA is not replaced by ASL, but ASL should be considered as a tool to facilitate the timing of follow-up DSA

studies, reduce the number of DSAs for each patient, and for the planning of additional AVM treatment.

Our study has several shortcomings, mostly inherent in its retrospective and noncontrolled design. Specifically, in our center, to optimize the SNR of the ASL sequence for AVMs detection,³⁴ we used a postlabeling delay of 1025 ms, shorter than the value typically recommended (1500 ms).³⁵ We chose this postlabeling because we have been using it since 2011, after local optimization with an excellent SNR across various cerebrovascular diseases. Second, this approach is very commonly used by experienced teams using ASL and has been validated extensively.³⁶

We also acknowledge that some patients have been lost to imaging follow-up following SRS outside our center, introducing some degree of attrition bias. Finally, these results were obtained in a sample of ruptured brain AVMs and may not be transferable to children with initially unruptured lesions.

CONCLUSIONS

In children with ruptured AVMs, ASL allows detection of hemodynamic changes after treatment, noninvasively and without radiation exposure or contrast media administration. Our results contribute data on the role of noninvasive ASL monitoring of the response of pediatric AVMs to treatment or follow-up after obliteration. Future research may help better elucidate how ASL can assist in decisions regarding optimal timing for DSA.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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