A cerebral arteriovenous malformation (AVM) is a tangle of blood vessels in the brain that comprises abnormally developed arterioles and venules without capillaries.\(^1,2\) AVMs are often asymptomatic but sometimes lead to cerebral hemorrhage, resulting in neurological sequelae and sudden death.\(^3\)–\(^5\) Craniotomy, endovascular surgery, and radiation therapy are treatment options for patients with AVMs who have a history of bleeding and for some patients with unruptured AVMs who are at high risk for bleeding.\(^2,5\)–\(^12\) Stereotactic radiosurgery (SRS) is a minimally invasive yet highly effective treatment method for patients with AVMs. Previous reports have demonstrated that SRS leads to obliteration of the AVM nidus at a rate of 60%–80% over 3–5 years, without increasing major complications.\(^13\)–\(^19\) However, there are cases in which single-session SRS does not lead to AVM obliteration. Since there is still a risk of bleeding with the presence of residual AVM, additional rounds of radiation are considered for such cases. Therefore, it is important to accurately assess the progress of AVM obliteration after SRS, as this will decide the later course of treatment.

Hemodynamic changes during the obliteration process for cerebral arteriovenous malformations after radiosurgery

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OBJECTIVE  The process of cerebral arteriovenous malformation (AVM) obliteration following radiosurgery is poorly understood. Authors of this retrospective study aimed to assess the changes in AVM hemodynamics after stereotactic radiosurgery (SRS) by using 3D flow magnetic resonance imaging (MRI) to elucidate the process of AVM obliteration.

METHODS  Twenty-four patients with AVMs treated with SRS between July 2015 and December 2017 were included in this study and classified into two groups depending on the duration of AVM obliteration: group A, obliteration within 3 years (n = 15); and group B, obliteration taking more than 3 years or no obliteration (n = 9). Blood flow (ml/min) in the largest feeding artery was measured before and after SRS by using time-averaged 3D flow MRI. The decreasing rate of blood flow in the feeding artery after SRS was calculated as the percent change from baseline blood flow. A Wilcoxon rank-sum test was used to compare the decreasing blood flow rate between the two groups at 4 and 12 months after SRS.

RESULTS  For the entire cohort, the mean decrease in blood flow in the feeding artery from baseline was 29% at 4 months and 71% at 12 months after SRS. In general, blood flow after SRS decreased faster in group A and slower in group B. The decreasing rates in blood flow at 4 and 12 months after SRS were significantly different between the two groups (p = 0.02 and < 0.001, respectively).

CONCLUSIONS  Tracking changes in AVM hemodynamics after SRS may be useful for assessing the progress of AVM obliteration and the therapeutic effects of SRS, possibly contributing to the prediction of subsequent obliteration outcome.

https://thejns.org/doi/abs/10.3171/2022.4.FOCUS2214

KEYWORDS  hemodynamics; arteriovenous malformations; stereotactic radiosurgery; magnetic resonance imaging

ABBREVIATIONS  AUC = area under the curve; AVM = arteriovenous malformation; DSA = digital subtraction angiography; IQR = interquartile range; MRA = MR angiography; MRI = magnetic resonance imaging; PC = phase contrast; ROC = receiver operating characteristic; SRS = stereotactic radiosurgery.


INCLUDE WHEN CITING  DOI: 10.3171/2022.4.FOCUS2214.
after SRS because of the possible neurological complications associated with this examination. Magnetic resonance imaging (MRI) has been used instead of DSA for routine post-SRS imaging. Several MRI sequences, such as dynamic arterial spin-labeling MR angiography (MRA) and time-resolved contrast-enhanced MRA, have been reported to be useful for confirming AVM obliteration. It is true that such MRI sequences can detect microscopic remnants of AVMs, but they cannot quantify the progress of AVM obliteration or the therapeutic effect of SRS on AVM hemodynamics. Time-averaged 3D flow MRI is a quantitative MRI method using phase contrast (PC) techniques and allows for the noninvasive measurement of flow parameters, such as mean blood flow in vessels.

In this study we aimed to assess the changes in AVM hemodynamics after SRS by using time-averaged 3D flow MRI to quantify the effect of SRS on AVM hemodynamics and to elucidate the process of AVM obliteration.

Methods

This retrospective study was approved by the Ethics Committee of The University of Tokyo. At the time of initial treatment, we obtained written informed consent from all patients for future use of their clinical data for research purposes.

Between July 2015 and December 2017 at our institution, 70 patients with AVMs were treated with SRS using the Leksell Gamma Knife (Elekta AB). To accurately assess the effect of SRS on AVM hemodynamics, we excluded 46 patients because of previous interventions for the AVM (n = 11), the use of multistaged SRS (n = 7), a small AVM volume (< 1 ml, n = 13), a lack of flow MRI data (n = 14), or an AVM with a very short feeder was inadequate for flow measurement (n = 1). Patients with previous interventions and multistaged SRS were excluded because of the possible influence of these factors on AVM hemodynamics. AVMs with a volume less than 1 ml were excluded because some of these small lesions were not well visualized on 3D flow MRI. Ultimately, 24 patients were included in the study and classified into group A (n = 15) and group B (n = 9). Group A was defined as those patients with AVM obliteration confirmed on both MRI and DSA within 3 years. (In 2 patients AVM obliteration was confirmed on MRI within 3 years, but DSA confirmation could only be performed after the 3-year point because of the examination schedule.) Group B was defined as those patients with residual AVMs on MRI or DSA after more than 3 years. Patients were separated into the two groups at 3 years because, as previously reported, during the examination schedule. Group B was defined as those patients with AVM obliteration confirmed on both MRI and DSA within 3 years. (In 2 patients AVM obliteration was confirmed on MRI within 3 years, but DSA confirmation could only be performed after the 3-year point because of the examination schedule.) Group B was defined as those patients with residual AVMs on MRI or DSA after more than 3 years. Patients were separated into the two groups at 3 years because, as previously reported, during the course of AVM treatment with SRS the median duration of AVM obliteration was 30–35 months.

Imaging

Time-averaged 3D flow MRI was performed with a 3-T scanner (Magnetom Skyra, Siemens) without a contrast agent and using a 20-channel head array coil. Imaging parameters for the 3D PC-MRI were as follows: TR 37.7 msec, TE 5.46 msec, number of excitations 2 (until July 2019) and 1 (since August 2019), flip angle 10°, generalized autocalibrating partial parallel acquisition (GRAPPA) factor 3, FOV 199 × 220 mm, matrix 348 × 384, voxel size 0.57 × 0.57 × 1 mm, slices 64 (until July 2019) and 128 (since August 2019), and bandwidth 365 Hz/pixel. The scan matrix was 174 × 194, and zero filling and the low-pass filter were applied for reconstruction of the matrix. The image data were corrected for Maxwell terms in online reconstruction. We set 100 cm/sec as velocity encoding in three directions (anterior-posterior, right-left, and superior-inferior) in all cases. The scan time regarding the time-averaged 3D flow MRI was 7.5 minutes. The MRI scans were obtained before SRS and approximately 4, 12, and 24 months after SRS.

Flow Analysis

All flow measurement was retrospectively performed using commercially available software (Amira, Thermo Fisher Scientific; and IV-FLOW, Maxnet Co., Ltd.). Amira was used to check for aliasing artifacts on flow MRI, and IV-FLOW was used to measure blood flow in vessels. To assess the obliteration process of AVMs, we focused on changes in blood flow (ml/min) in the largest feeding artery before and after SRS (Fig. 1). The feeding artery with the most developed flow on pre-SRS MRI was defined as the largest feeding artery, was selected as the target. The measurement point was placed at the periphery of the largest feeding artery, before the AVM nidus. IV-FLOW is software that can analyze blood flow using 3D or 4D flow MRI, and when segmenting blood vessels using the region-growing method, it automatically extracts the centerline of the vessel. By setting the perpendicular plane on the centerline, users can quantify blood flow at any point in vessels. The entire work was performed by the first author (Y.T.), who is a board-certified neurosurgeon with more than 3 years of experience in flow MRI research of the brain. In addition to blood flow measurement, the decreasing rate of blood flow in the feeding artery after SRS was calculated as a percentage of the pretreatment flow.

Statistical Analysis

All statistical analyses were conducted using JMP 16 (SAS Institute Inc.). The decreasing rates of blood flow in the feeding artery at 4 and 12 months after SRS were compared between groups A and B by using the Wilcoxon rank-sum test. In addition, logistic regression analysis and receiver operating characteristic (ROC) curve analysis were performed to stratify the prognosis of AVM obliteration (group A vs B) based on the decreasing blood flow rates in the feeding artery at 4 and 12 months after SRS. In the ROC curve analysis, the optimal cutoff point of the diagnostic potential was determined using the Youden index. A p value < 0.05 was considered significant.

Results

Clinical characteristics and radiosurgical dosimetry data are presented in Table 1; there were no statistically significant differences between groups A and B.

The relationship between blood flow in the feeding artery and time course after SRS is displayed in Fig. 2.
and the detailed values are listed in the Supplementary Data. For the entire cohort, the mean decrease (median, interquartile range [IQR]) in blood flow in the feeding artery from baseline was 29% (24%, 14%–43%) at 4 months and 71% (72%, 44%–100%) at 12 months after SRS. In general, blood flow in the feeding artery decreased faster in group A and slower in group B after SRS. The mean decrease (median, IQR) in blood flow in the feeding artery from baseline was 35% (30%, 22%–52%) in group A and 19% (17%, 11%–24%) in group B at 4 months (p = 0.02) and 90% (100%, 78%–100%) in group A and 49% (44%, 34%–69%) in group B at 12 months after SRS (p < 0.001; Table 2). Seven patients in group B whose blood flow decreased to 0 within 3 years have been confirmed to have residual AVM on other MRI sequences or DSA. One case from group B had AVM obliteration confirmed on MRI, but subsequent DSA showed residual AVM.

Logistic regression analysis demonstrated that the decreasing rate at 4 months after SRS was significantly associated with the prognosis of AVM obliteration (p = 0.01). According to ROC curve analysis, the area under the curve (AUC) was 0.79, and the optimal cutoff point of the decreasing rate at 4 months after SRS was 0.25. Based on the optimal cutoff point, diagnostic performance is as follows: sensitivity of 88.9%, specificity of 66.7%, positive predictive value of 61.5%, positive predictive value of 61.5%, and negative predictive value of 90.9%. Similarly, logistic regression analysis demonstrated that the decreasing rates at 12 months after SRS were significantly associated with the prognosis of AVM obliteration (p < 0.001). The AUC of the ROC curve analysis was 0.97, and the optimal cutoff point of the decreasing rate at 12 months after SRS was 0.72. Based on the optimal cutoff point, diagnostic performance is as follows: sensitivity

**FIG. 1.** A representative case from group B. Time-averaged 3D flow MRI with streamline visualization at multiple time points, showing intracranial circulation with the AVM in the left temporal lobe. The measurement point is placed at the periphery of the feeding artery, just before the AVM nidus. A: Before treatment. Two feeding arteries (asterisk, largest feeding artery; arrowhead, other feeding artery), an AVM nidus (dagger), and a draining vein (double dagger) are visible. B: At 178 days after treatment. The AVM nidus is poorly delineated and the draining vein has shrunk, as compared to their appearance before treatment. Regarding the feeding arteries (asterisk and arrowhead), there are no significant changes. C: At 388 days after treatment. The AVM nidus and draining vein have almost disappeared. Two feeding arteries (asterisk and arrowhead) are indicated but have shrunk compared to their appearance in panels A and B. D: At 761 days after treatment. The largest feeding artery (asterisk) is depicted faintly, and the other feeding artery (arrowhead) has disappeared. Blood flow in the largest feeding artery at each time point was 86, 50, 24, and 7 ml/min, respectively.
of 100%, specificity of 90.0%, positive predictive value of 90.0%, and negative predictive value of 100%.

**Discussion**

In the present study, the changes in AVM hemodynamics after SRS were assessed quantitatively by tracking changes in blood flow in the largest feeding artery to the AVM. Our results suggest that the assessment of AVM hemodynamics by time-averaged 3D flow MRI is useful for quantifying the progress of AVM obliteration or the therapeutic effect of SRS treatment.

**TABLE 1. Clinical characteristics and radiosurgical dosimetry data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>15</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Mean age in yrs (range)</td>
<td>38 (12–65)</td>
<td>45 (19–72)</td>
<td>0.31*</td>
</tr>
<tr>
<td>Female sex</td>
<td>6 (40%)</td>
<td>4 (44%)</td>
<td>0.99*</td>
</tr>
<tr>
<td>History of hemorrhage</td>
<td>2 (13%)</td>
<td>0</td>
<td>0.51†</td>
</tr>
<tr>
<td>Spetzler-Martin grade</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>I</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>IV–V</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mean AVM vol in ml (median, range)</td>
<td>4.0 (3.4, 1.5–13.4)</td>
<td>4.7 (2.3, 1.3–12.8)</td>
<td>0.93*</td>
</tr>
<tr>
<td>Eloquent location</td>
<td>9 (60%)</td>
<td>5 (56%)</td>
<td>0.99†</td>
</tr>
<tr>
<td>Deep venous drainage</td>
<td>2 (13%)</td>
<td>2 (22%)</td>
<td>0.61†</td>
</tr>
<tr>
<td>AVM location</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>Supratentorial superficial</td>
<td>12</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Infratentorial</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Deep seated</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Mean central dose in Gy (median, range)</td>
<td>39.8 (40.0, 33.3–50.0)</td>
<td>37.1 (37.0, 34.3–40.0)</td>
<td>0.06*</td>
</tr>
<tr>
<td>Mean margin dose in Gy (median, range)</td>
<td>19.6 (20.0, 18.0–20.0)</td>
<td>19.1 (19.0, 18.0–20.0)</td>
<td>0.12*</td>
</tr>
<tr>
<td>Virginia Radiosurgery AVM Scale score</td>
<td></td>
<td></td>
<td>0.63†</td>
</tr>
<tr>
<td>0–2</td>
<td>12 (80%)</td>
<td>6 (67%)</td>
<td></td>
</tr>
<tr>
<td>3–4</td>
<td>3 (20%)</td>
<td>3 (33%)</td>
<td></td>
</tr>
</tbody>
</table>

* Calculated using the Wilcoxon rank-sum test.
† Calculated using Fisher’s exact test.

**FIG. 2.** A line graph of the relationships between blood flow in the feeding artery and time course after SRS. The vertical axis shows the rate of change in blood flow in the largest feeding artery when blood flow before treatment is set to 1. The horizontal axis shows the passage of time (days). The *pink* and *blue lines* indicate groups A and B, respectively.
There is no established way to quantify the progress of AVM obliteration or the therapeutic effect of SRS on AVMs; thus, in each follow-up, physicians evaluate the morphological changes in AVMs on routine MRI. Srinivas et al. compared hemodynamic and morphological changes in AVMs after SRS by using MRI, including time-resolved 3D flow.30 Their results showed that the hemodynamic changes were significantly different before and after SRS, even though some morphological features, such as the diameter of the feeding artery and the AVM volume, were not significantly different before and after SRS. They mentioned the possibility that hemodynamic changes in AVMs precede morphological changes. Our results are consistent with their results. In the present study, patients with AVMs were classified into two groups based on the response to SRS, and significant differences in AV hemodynamics emerged between the two groups at 4 and 12 months after SRS, which was long before morphological obliteration could be identified. Therefore, tracking changes in AVM hemodynamics after SRS may help to predict subsequent obliteration outcome since changes in AVM hemodynamics may precede morphological changes.

The importance of evaluating changes in AVM hemodynamics was also reported by Alaraj et al.31 These authors successfully observed significant changes in AVM hemodynamics associated with embolization using 2D PC-MRI with NOVA software (VasSol Inc.). Their results showed how AVM flow is reduced through multiple embolization sessions, and their research design was similar to ours. Observing hemodynamic changes using flow MRI may help to discover new hemodynamic biomarkers. In our study, we investigated whether the decreasing rate of blood flow in the feeding artery at 4 and 12 months could predict the prognosis of obliteration outcome (group A vs B) by using ROC curve analysis. The optimal cutoff points of the decreasing rates at 4 and 12 months were 0.25 and 0.72, respectively. It would be ideal to be able to predict future obliteration and its time course because the latency period, or a period from SRS to AVM obliteration, is largely dependent on each case. Our results demonstrated that a decrease of blood flow in the feeding artery less than 0.72 at 12 months after SRS indicated a low likelihood of AVM obliteration within 3 years of SRS, suggesting the usefulness of 3D flow MRI in assessing AVM hemodynamics.

To date, little is known about the temporal changes in AVMs following SRS. Schneider et al. described the pathological findings in AVMs after SRS.32 Their results demonstrated that the pathological sequence of changes began with damage to the endothelial membrane, leading to hyaluronic acid sclerosis with the proliferation of intimal smooth muscle cells and production of collagen and eventual occlusion of the vessel wall structure. These findings correlated well with time after irradiation and with size reduction shown on imaging. The results of our study were consistent with these findings. In our study, blood flow in the feeding artery decreased by 29% at 4 months and by 71% at 12 months after SRS in the entire cohort, with significant differences in the decrease of blood flow between groups A and B. Since AVM volume and AVM inflow are highly correlated,36 the decrease in blood flow in the feeding artery may reflect radiation-induced pathological changes in the AVM, particularly the decrease in AVM volume associated with eventual occlusion of the microvessels.

Of note, the speed of the decrease in blood flow in the feeding artery was not uniform in many cases. In group A, there were cases in which the flow decrease was slow at first but then became faster until obliteration, and vice versa. The process that leads to obliteration of the AVM nidus after SRS is not completely understood, but it has been reported to involve occasional thrombi in addition to the vessel narrowing over time.32 The occasional thrombi in the AVM could be related to a sudden decrease in blood flow in the feeding artery. Furthermore, in most cases, the blood flow decreased to 0 during the observation period of about 1000 days. This result may represent the decreasing risk of hemorrhage post-SRS. Although previous studies have reported that the decrease in post-SRS hemorrhage was caused only by AVM obliteration,16,33,34 it is also possible that the decrease in AVM blood flow may cause a decrease in AVM pressure, resulting in fewer bleeding events. Further research is warranted to elucidate the mechanism of AVM bleeding and obliteration after SRS.

**Study Limitations**

There are several limitations to the present study. First, although blood flow in the largest feeding artery was measured to assess the obliteration process of AVMs in
this study, there are other possible methods. Blood flow in draining veins may also be a good predictor of AVM obliteration; however, the accuracy of the quantified venous flow would be less reliable than that of arterial flow because of the high velocity-encoding setting (100 cm/sec) employed in this study. Further, measuring blood flow in multiple feeding arteries may theoretically be more accurate; however, it would be less feasible in clinical practice because it is quite time-consuming. Moreover, as shown in the representative case, even if there were multiple feeding arteries, all of them tended to shrink and disappear at a similar rate in most cases. Therefore, to balance feasibility and accuracy, we focused on blood flow in the largest feeding artery.

Second, it is known that the accuracy of quantifying blood flow by 3D flow MRI is reduced when blood flow is much lower than the velocity encoding.25,36–38 Indeed, it would have been ideal to change the velocity encoding in accordance with the blood flow velocity. However, in this study the velocity encoding was fixed at 100 cm/sec for smooth workflow. Third, the relatively small sample size of this study precludes strong conclusions. However, the relatively long follow-up of the AVM hemodynamics after SRS is worthwhile. Finally, since our study population mainly consisted of patients with small- to medium-sized AVMs, the results may not be applicable to all patients with AVMs.

Conclusions

In this study we revealed the changes in AVM hemodynamics after SRS by using time-averaged 3D flow MRI. The changes in AVM hemodynamics were significantly different at 4 and 12 months after SRS, depending on the response to SRS. Tracking changes in AVM hemodynamics after SRS may be useful for assessing the process of AVM obliteration and the therapeutic effects of SRS, possibly contributing to the prediction of subsequent obliteration outcome.

Acknowledgments

Dr. Kin has received grant support from the Japan Society for the Promotion of Science KAKENHI (grant no. JP21K09095) and Japan Science and Technology Agency CREST (JPMJCR17A1).

References


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: Takeda. Acquisition of data: Hasegawa, Takeda, Shinya, Kawashima, Furuta, Suzuki. Analysis and interpretation of data: Takeda, Furuta, Sekine, Saito. Drafting the article: Takeda. Critically revising the article: Hasegawa, Shinya, Furuta, Sekine, Saito. Reviewed submitted version of manuscript: Hasegawa, Kin, Shinya, Kawashima, Suzuki, Sekine, Saito. Approved the final version of the manuscript on behalf of all authors: Hasegawa. Statistical analysis: Takeda, Shinya, Sekine. Administrative/technical/material support: Hasegawa, Kin, Shinya, Kawashima, Suzuki, Sekine, Saito. Study supervision: Hasegawa, Kin, Saito.

Supplemental Information
Online-Only Content

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