Relative signal intensity on time-of-flight magnetic resonance angiography as a novel indicator of aggressive presentation of intracranial dural arteriovenous fistulas

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Abstract

Asymptomatic dural arteriovenous fistulas (DAVFs) with cortical venous reflux (CVR) are now more commonly encountered. However, patients with an incidental onset may have a less aggressive clinical course. It is desirable to explore methods and indicators to predict the clinical outcomes. This study investigates whether the relative signal intensity (rSI) of the draining vessels on the time-of-flight magnetic resonance angiography is related to clinical behavior in patients with intracranial DAVFs. We retrospectively reviewed 36 intracranial DAVFs. The patients were categorized as those with either aggressive-presentation or non-aggressive-presentation ($n = 16$ and 20 , respectively). The rSIs of the shunt points, affected sinuses, and veins with CVR were compared between the two groups. The two groups were not significantly different in terms of rSIs of the shunt points and affected sinuses ($p = 0.37$ and 0.41 , respectively). However, a significant positive correlation was observed in the rSI of the veins with CVR between the aggressive and non-aggressive behavior groups ($p < 0.0001$). The rSI of the veins with CVR could serve as a reliable indicator of aggressive behavior in intracranial DAVFs, and its optimal cutoff value was 1.63 with high sensitivity and specificity for predicting aggressive behavior (area under the curve, 0.909).

Keywords

arteriovenous fistula, central nervous system vascular malformations, hyperemia, magnetic resonance angiography, magnetic resonance imaging

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Introduction

Intracranial dural arteriovenous fistulas (DAVFs) are generally classified based on the pattern of venous drainage.^{1,2} Particularly, cortical venous reflux (CVR) is accepted as a risk of aggressive DAVF behavior, including the possibility of intracranial hemorrhage (ICH) and non-hemorrhagic neurological deficits (NHND).^{1–6} As CVR is closely related to cerebral hemodynamic and metabolic disturbance in DAVF and blood volume increases in the cerebral hemisphere with CVR in DAVF,^{7,8} it has been suggested that angiographic findings of retrograde venous drainage into the cortical veins and delayed parenchymal circulation are important predictors of the hemodynamic

status of intracranial DAVFs.^{9–12} Therefore, the greater the extent of reflux into the cortical veins, the more severe is the impairment of the cerebral venous

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drainage. The severity and development of aggressive presentation could be predicted by estimating the degree of retrograde venous reflux in patients with DAVFs.

Accordingly, we hypothesized that the relative signal intensity (rSI) of the drainage vessels measured using the time-of-flight magnetic resonance angiography (TOF-MRA) can reflect the flow velocity and blood volume of the reflux in DAVFs.^{13,14} However, no reports have quantitatively evaluated the degree of CVR based on imaging findings or verified the capacity of rSI to represent the clinical behavior of DAVFs. We hypothesized that the rSI of the veins with CVR on TOF-MRA would reflect the degree of reflux and correlate with the measures of clinical presentation of intracranial DAVFs. Therefore, we aimed to determine whether the rSI of the drainage vessels on non-invasive TOF-MRA can be used as a marker to distinguish between aggressive and non-aggressive DAVF presentations. Additionally, to clarify the relationship between the rSI and clinical presentation, the optimal cutoff values for rSI for predicting the clinical outcome were determined.

Material and methods

All procedures performed in this series involving human participants were in accordance with the ethical standards of the institutional research committee (Saint Luke's International Hospital, No. 19-R200) and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The need for written informed consent was waived because of the retrospective design of the study. The STROBE guidelines have been followed in this manuscript.

Patient selection and subjects

This retrospective study included 40 consecutive patients diagnosed with intracranial DAVFs between January 2015 and May 2020. Of these, the data of 36 patients were analyzed for whom both preoperative TOF-MRA and conventional digital subtraction angiography (DSA) data were available.

The diagnosis and detailed angioarchitecture of intracranial DAVFs were evaluated based on DSA combined with TOF-MRA by well-experienced interventional neuroradiologists. Data were also collected from the medical records. Demographic data, baseline clinical status, and imaging results were analyzed for all patients. The DAVFs were further classified based on the Borden¹ and Cognard² classifications according to the venous drainage pattern.

The patients were divided into two groups, namely an aggressive-presentation and a non-aggressive-presentation groups of patients who developed ICH,

NHND—including dementia and venous infarction—and seizures caused by severe venous hypertension and patients with other clinical symptoms, including headache, tinnitus, chemosis, dizziness, and incidental onset, respectively. These groups were compared for the rSI of the shunt points, affected sinuses, and veins with CVR.

Imaging

MR imaging (MRI) was performed on a 3.0-Tesla imaging system (Discovery MR750w, GE Healthcare, Milwaukee, WI). The parameters of TOF-MRA were slice thickness, 1.0 mm; repetition/echo times, 22/3.6 ms; flip angle, 8°; field of view, 200 × 180 mm; and acquisition matrix, 416 × 224. The duration of TOF-MRA was 4 minutes 18 seconds. A 12-channel head radiofrequency coil was used for all patients.

A biplane angiography system (Artis zee Q, Siemens Healthcare GmbH, Forchheim, Germany) was used for the conventional DSA. In addition to the conventional DSA, a three dimensional (3D)-rotational angiography was subsequently performed. The 3D data obtained were reconstructed into thin slab-maximum intensity projection (MIP) and multiplanar reconstruction images. The angioarchitecture, including shunt location, feeders, drainers, and anatomical evaluation, was analyzed in detail.

Data analysis and image processing

We retrospectively examined the obtained TOF-MRA and DSA data. The angioarchitecture of the DAVF was prospectively evaluated using the DSA. Venous drainage into the dural venous sinus and CVR with venous drainage directly into the cortical veins (Borden grade II or III; Cognard grade IIb, IIa+b, III, or IV)^{1,2} were evaluated. A region of interest (ROI) analysis was performed, and the SI was measured from the TOF-MRA MIP source image using ImageJ/FIJI (National Institutes of Health, Bethesda, MD). During image analysis, the target vessels that were not clearly delineated by artifacts on TOF-MRA were excluded from the analysis. In setting the ROIs, the anatomical location of the shunt points and veins were colocalized based on the DSA or 3D-rotational angiography MIP source imaging. Accordingly, an affected sinus and a vein with CVR were defined as the drainage route of a shunt presenting abnormally high SI and vein with retrograde venous drainage presenting abnormally high SI, respectively, were extracted on TOF-MRA. Each ROI covering the vessel lumen or temporal muscle was outlined. The mean SI at the shunt points, affected sinuses, veins with CVR, and temporal muscles were measured in each case (Figures 1 and 2). We adopted a perfectly circular shape for all ROIs. Each ROI was set to be no larger

Figure 1. Illustrative case 1. A 42-year-old woman diagnosed with transverse-sigmoid sinus DAVF presented with tinnitus (non-aggressive presentation). TOF-MRA [(a) A-P view, (b) lateral view] and left occipital artery angiography [(c) A-P view, (d) lateral view] images show Borden type III DAVF and marked CVRs. Representative TOF-MRA MIP image of the region of interest set (orange circle) in the temporal muscle (e), shunt point (f), affected sinus (g), and vein of Labbe with CVR (h). The rSI of the vein of Labbe with CVR is 1.55.

A-P: anterior-posterior; CVR: cortical venous reflux; DAVF: dural arteriovenous fistula; MRA: magnetic resonance angiography; MIP: maximum intensity projection; rSI: relative signal intensity; TOF: time-of-flight.

than the target vessels or the target temporal muscles. The ROI size changed according to the vessel of interest. The same ROI size was set for the temporal muscle in all cases. For the semiquantitative analysis, the rSI was used for assessing the degree of the shunt flow. The ratio of the mean SI of the relevant vessel to the mean SI of the patient's temporal muscle (SI_m) was considered the rSI. The rSI was calculated using the following algorithm: rSI of the shunt point = mean SI of the relevant shunt point/ SI_m ; rSI of the affected sinus = mean SI of the affected sinus/ SI_m ; and rSI of the vein with CVR = mean SI of the relevant vein with CVR/ SI_m .

To calculate the rSI, the temporal muscle was selected as the denominator for the rSI reference. It was compared to the backgrounds used as the denominator (see Supplemental Material), the temporal muscles can be used more reliably for this purpose and present a uniform SI with limited individual variations.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation and categorical variables are expressed as number and percentage. When comparing the two groups, categorical variables were evaluated using Pearson's chi-squared test and continuous variables

were evaluated using Welch's *t*-test. Between-group comparison of the rSI of the shunt points, affected sinuses, and veins with CVR was performed using the Welch's *t*-test. We evaluated the relationship of each rSI between the aggressive- and non-aggressive-presentation groups to determine whether rSI could be an indicator of aggressive presentation. All statistical analyses were performed using JMP Pro13 (SAS Institute, Cary, NC, USA). The significance level was set at $p < 0.05$.

Receiver operator characteristic (ROC) curves were constructed to obtain the optimal cutoff values for the rSI of the veins with CVR for predicting aggressive presentation. The optimal cutoff value was estimated using the Youden index. The sensitivity, specificity, and positive and negative predictive values were calculated for predicting aggressive presentation. The areas under the ROC curve (AUC) were also determined to confirm the predictive and diagnostic abilities of the ROC curve.

Results

Patient demographics and intracranial DAVF characteristics

The patient demographics and DAVF characteristics are summarized in Table 1. Aggressive presentation

Figure 2. Illustrative case 2. A 69-year-old woman diagnosed with transverse-sigmoid sinus DAVF presented with intracerebral hemorrhage (aggressive presentation). TOF-MRA [(a) A-P view, (b) lateral view] and left occipital artery angiography [(c) A-P view, (d) lateral view] images show Borden type III DAVF and marked CVRs. Representative TOF-MRA MIP image of the region of interest set (orange circle) in the temporal muscle (e), shunt point (f), occipital vein with CVR (g), and middle temporal vein with CVR (h). The rSI of the middle temporal vein with CVR is 2.21.

A-P: anterior-posterior; CVR: cortical venous reflux; DAVF: dural arteriovenous fistula; MRA: magnetic resonance angiography; MIP: maximum intensity projection; rSI: relative signal intensity; TOF: time-of-flight.

was observed in 16 patients, and non-aggressive presentation in 20 patients. The patients of both groups were well-matched for age, Borden classification, Cognard classification, and location of the shunt. A significant difference was observed in sex, as there were significantly more female patients in the aggressive-presentation group (11 female [68.7%] vs 7 female [35.0%] patients, $p = 0.04$).

Association between the rSI and clinical DAVF presentation

In the aggressive-presentation group, 16 affected sinuses and 28 veins with CVR were extracted. In the non-aggressive-presentation group, 18 affected sinuses and 22 veins with CVR were extracted (Table 2). No significant intergroup difference was found in the mean rSI of the temporal muscles (i.e., mean SI of the temporal muscle/mean SI of the background), which was used as a reference (3.93 ± 1.52 vs 4.10 ± 1.87 , $p = 0.77$).

The difference between the aggressive- and non-aggressive-presentation groups was nonsignificant in terms of the mean rSI of the shunt points (2.19 ± 0.70 vs 1.98 ± 0.64 , $p = 0.37$) or affected sinuses (2.30 ± 0.70 vs 2.08 ± 0.85 , $p = 0.41$; Table 2 and Figure 3(a) and

(b)). The mean rSI of the veins with CVR in the aggressive-presentation group was significantly higher than that in the non-aggressive-presentation group (2.15 ± 0.62 vs 1.36 ± 0.30 , $p < 0.0001$; Table 2 and Figure 3(c)).

Optimal cutoff value of the rSI

ROC analysis of the rSI of the veins with CVR was performed to distinguish aggressive presentation from non-aggressive presentation in intracranial DAVF (Figure 4(a) and (b)). The optimal cutoff value identified from the ROC curve was 1.63 (AUC, 0.90909) for the maximum sensitivity and specificity for rSI (Figure 4(b)). The sensitivity, specificity, positive predictive value, and negative predictive value were 89.2%, 86.3%, 89.2%, and 86.3%, respectively.

When the rSI was calculated using the background as the denominator, only the veins with CVR also constituted a significant factor of aggressive presentation (see Supplemental Figure 1). However, the AUC calculated based on the backgrounds was smaller than that calculated based on the temporal muscles (0.81981 vs 0.90909, Figure 4 and Supplemental Figure 1). Therefore, in this study, we adopted an rSI with high

Table 1. Characteristics of patients with dural arteriovenous fistula.

Variable	Aggressive presentation	Non-aggressive presentation	p value
No. of patients	16	20	
Age (years)	58.4 ± 4.5	64.0 ± 4.0	0.40
Male / Female	5 (31.3%)/11 (68.7%)	13 (65.0%)/7 (35.0%)	0.04
Clinical presentation	—	—	< 0.0001
Hemorrhagic onset	4 (25.0%)	0 (0%)	
Seizures	6 (37.5%)	0 (0%)	
NHND	6 (37.5%)	0 (0%)	
Non-aggressive symptoms	0 (0%)	13 (65.0%)	
Asymptomatic	0 (0%)	7 (35.0%)	
Borden classification	—	—	0.24
I	1 (6.2%)	5 (25.0%)	
II	10 (62.5%)	8 (40.0%)	
III	5 (31.3%)	7 (35.0%)	
Cognard classification	—	—	0.30
I	0 (0%)	2 (10.0%)	
2a	3 (18.7%)	6 (30.0%)	
2a+b	8 (50.0%)	5 (25.0%)	
3	5 (31.3%)	7 (35.0%)	
Location	—	—	0.38
Cavernous sinus	6 (37.4%)	5 (25.0%)	
Transverse/sigmoid sinus	5 (31.2%)	6 (30.0%)	
Jugular vein	0 (0%)	1 (5.0%)	
Jugular tubercle venous complex	0 (0%)	1 (5.0%)	
Middle fossa	1 (6.3%)	0 (0%)	
Tentorium	1 (6.3%)	5 (25.0%)	
Convexity	2 (12.5%)	0 (0%)	
Anterior cranial fossa	0 (0%)	1 (5.0%)	
Superior sagittal sinus	1 (6.3%)	1 (5.0%)	

Values are expressed as mean ± standard deviation for quantitative variables or as absolute number (percentage) for qualitative variables. NHND: non-hemorrhagic neurological deficits.

Table 2. Magnetic resonance angiography relative signal intensity of dural arteriovenous fistula.

Variable	Aggressive presentation	Non-aggressive presentation	p value
No. of patients	16	20	
Shunt pouch	16	20	
Affected sinuses	16	18	
Veins with CVR	28	22	
Mean rSI			
Shunt points	2.19 ± 0.70	1.98 ± 0.64	0.37
Affected sinuses	2.30 ± 0.70	2.08 ± 0.85	0.41
Veins with CVR	2.15 ± 0.62	1.36 ± 0.30	< 0.0001

Values are expressed as mean ± standard deviation for quantitative variables or percentage for qualitative variables. rSI: relative signal intensity; CVR: cortical venous reflux.

discrimination ability, which was calculated using the mean SI of the temporal muscle as reference.

Illustrative cases

Case 1: A 42-year-old woman who was diagnosed with a transverse-sigmoid sinus DAVF presented with tinnitus (non-aggressive presentation). A Borden type III DAVF, with marked CVRs and an isolated sinus,

was identified (Figure 1(a) to (h)). The rSI of the vein of Labbe with CVR was 1.55 (Figure 1(h)).

Case 2: A 69-year-old woman who was diagnosed with transverse-sigmoid sinus DAVF presented with ICH of the temporal lobe (aggressive presentation). Borden type III DAVF with marked CVRs and isolated sinus was determined (Figure 2(a) to (h)). The rSI of the middle temporal vein with CVR was 2.21 (Figure 2(h)).

Figure 3. Comparison of rSI in patients with intracranial DAVFs. Association between rSI measured on TOF-MRA and the clinical presentation of DAVFs. There is no significant difference in the mean rSI of the shunt points (a) and the mean rSI of the affected sinuses (b) in the aggressive- and non-aggressive-presentation groups. The mean rSI of the veins with CVR (c) is significantly higher in the aggressive-presentation group than in the non-aggressive-presentation group. Green rhomboids indicate the 95% confident intervals. The line across the center of each rhombus represents the group average. The blue lines represent ± 1 SD. CVR: cortical venous reflux; DAVF: dural arteriovenous fistula; TOF-MRA: time-of-flight magnetic resonance angiography; ns: not significant; rSI: relative signal intensity; SD: standard deviation.

Figure 4. Optimal cutoff value of the rSI determined from the ROC curve analysis. (a) Logistic probability plot showing the rSI of the veins with CVR in patients with intracranial DAVF with aggressive and non-aggressive presentation. (b) ROC curve analysis of the rSI of the veins with CVR for distinguishing between aggressive and non-aggressive presentation in patients with intracranial DAVFs. The optimal cutoff value for obtaining the maximum sensitivity and specificity is 1.63 (AUC, 0.90909). The sensitivity, specificity, positive predictive value, and negative predictive value are 89.2%, 86.3%, 89.2%, and 86.3%, respectively. AUC: area under the curve; CVR: cortical venous reflux; DAVF: dural arteriovenous fistula; ROC: receiver operating characteristic; rSI: relative signal intensity.

Discussion

In this study, we investigated whether the rSI of the draining vessels determined using TOF-MRA is related to clinical behavior in patients with intracranial DAVFs. The mean rSI of the veins with CVR was significantly higher in the aggressive-presentation than in the non-aggressive-presentation group. Increased CVR may result in increased SI of the veins with CVR on TOF-MRA. Additionally, we determined the optimal cutoff rSI values with high sensitivity and specificity for predicting aggressive behavior. To the best of our knowledge, this was the first study to confirm that rSI is a useful noninvasive tool for evaluating the clinical presentation of intracranial DAVFs.

As SI on TOF-MRA depends on the number of moving spins (saturation effect), the velocity of blood

flow and blood volume affect the SI, with faster blood flow generally resulting in higher SI and slower blood flow resulting in lower SI.¹⁴ Using this theory, semiquantitative evaluation methods using the SI ratio have been reported as an indirect indicator to assess cerebral perfusion and cerebral hemodynamic status.^{13,15,16} However, no reports have quantitatively evaluated the degree of CVR in intracranial DAVFs based on imaging findings. Accordingly, we focused on the fact that SI on TOF-MRA reflects the flow velocity and degree of the shunt and proposed a semiquantitative method to evaluate the degree of reflux.

The neurological symptoms and risks associated with intracranial DAVFs depend on the venous drainage pattern.¹⁷ A restricted venous drainage route such as stenosis or thrombosis of the venous outflow results in conversion to aggressive DAVF by increasing the

reflux shunt into the cortical veins.^{17,18} In intracranial DAVFs with CVR, dynamic susceptibility-weighted contrast-enhanced perfusion MRI revealed an increase of cerebral blood volume at the hemisphere with CVR.^{7,8} The present results, a high rSI of the veins with CVR was strongly correlated with aggressive DAVF behavior, may indirectly reflect the fact that severe venous hypertension causes cerebral hemodynamic and metabolic disturbances.^{7-9,19}

Intracranial DAVFs with CVR have been associated with a high incidence of serious adverse events and poor outcomes.⁶ However, in recent years, lower adverse event rates have been reported for asymptomatic DAVFs with CVR,^{5,20} and symptomatic CVR has been considered an important factor for severe neurological events.^{5,20-22} With the recent advances in neuroradiological examination, encountering asymptomatic DAVFs with CVR has become more common. Meanwhile, even asymptomatic DAVFs with CVR may develop aggressive behavior later.^{6,23,24} They have been identified to have elevated cerebral blood volume in the affected area, including risk of deterioration.^{7,8} In some cases of asymptomatic CVR, the reflux will gradually increase, and cerebral circulation and metabolism will deteriorate in the long term.⁶ Thus, a more judicious approach towards therapeutic intervention is warranted. It is desirable to explore indicators that can be used to evaluate the clinical outcome and delineation of groups with aggressive conversion risk. However, a reliable evaluation method to decide the appropriate timing for therapeutic intervention cannot be established.

Some studies have evaluated cerebral hemodynamics and cerebral metabolism in patients with intracranial DAVFs with CVR using positron emission tomography, single photon emission computed tomography, perfusion MRI, arterial spin labeling perfusion imaging, and MR spectroscopy.^{7-11,19,25} These reports have indicated that accompanying CVR can lead to reduced regional cerebral blood flow, increased cerebral blood volume, elevated regional oxygen extraction fraction, and impaired cerebral circulation and metabolism.^{9-11,19} Therefore, imaging follow-up with several modalities is essential for identifying the changes associated with aggressive DAVF behavior. DSA is the standard modality for the diagnosis and evaluation of the angioarchitecture and hemodynamic impairment in patients with DAVFs.²⁶ However, it is not suitable as a follow-up tool given that it is invasive and the patient is exposed to radiation. Conversely, given that TOF-MRA is noninvasive, repeatable, and readily available it can be used as an evaluation tool for monitoring during the follow-up period. The rSI can be easily measured using TOF-MRA, and the measurements are highly reproducible; thus, the rSI could serve as an

indicator for the development of aggressive behavior in the future.

This study had some limitations. First, this was a retrospective study with a relatively small sample size and potential selection biases. Therefore, the generalization of the conclusions of this study may be limited. As the present results were derived from limited locations, the mode of presentation may have varied depending on the location of the intracranial DAVFs.²⁷ Here, the patient characteristics were well-matched between the aggressive- and non-aggressive-presentation groups except for the sex. The high prevalence of cavernous sinus DAVFs among those with aggressive presentation may have affected the observed sex difference. Second, the MR imaging parameters influence the saturation effect on TOF-MRA, leading to a change in SI.¹⁴ Therefore, there is need to minimize the acquisition parameters and scanner-related and inter-facility differences. Some studies have addressed these issues by reporting the interobserver reproducibility of the SI ratio on TOF-MRA using different software programs and the validity of rSI measured at different strengths (1.5 and 3-Tesla)/MRI scanners.^{13,15,16,28} Thus, evaluation by rSI would be more generalizable. Third, SI is also affected by several factors other than blood-flow velocity, such as vessel stenosis, vessel orientation, tortuosity, and turbulent flow.¹⁴ Ghost artifacts caused by periodic movement (e.g. arterial or CSF pulsations) affect the image clarity, and their intensity is not affected by the peak flow velocity, but is dependent on the pulse rates, TR values, and flip angles in the MRI settings.¹⁴ Image settings with fewer artifacts are more important. Moreover, selecting and placing ROIs require experience and anatomical knowledge. Manual placement of the ROI may affect the SI-related results. To minimize interobserver differences, assessment using the rSI as a relative, rather than an absolute, value measured on TOF-MRA may be more generalizable. Naturally, a question remains whether rSI could predict the long-term clinical outcome, as this study did not examine rSI changes over long-term periods. Direct comparison between the rSI of the veins with CVR and cerebral circulation/metabolism may be necessary in the future. Thus, further studies are also needed to confirm whether rSI could be a simpler and reliable indicator for predicting the development of aggressive behavior in intracranial DAVFs. Although some challenges remain, the vessel rSI measurement on TOF-MRA shows promise as a potential indicator of clinical outcomes in intracranial DAVF. The rSI of the veins with CVR measured on TOF-MRA may serve as a reliable indicator of aggressive behavior. This parameter could be used as a noninvasive follow-up tool to determine

the exact treatment timing for intracranial DAVF with CVR carrying a risk for severe neurological events.

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Declaration of conflicting interests

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Authors' contributions

BR initiated the project in this manuscript. BR and YN wrote the manuscript. BR, SS, TM and YN participated in the treatment, discussed the results, and approved the final version of the manuscript.

Supplemental material

Supplemental material for this article is available online.

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