의학석사 학위논문

# Intracranial arteriovenous malformation:

## Semiquantitative analysis of arterial spin labeling magnetic resonance imaging in correlation with digital subtraction angiography

# 두개강내 동정맥 기형:

## 동맥스핀라벨링 자기공명영상기법에서의 정맥동 신호강도에 대한 감산혈관조영술과의 준정량적 상관분석

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선 우 준

A thesis of the Master's Degree

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August 2014

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이 논문을 의학석사 학위논문으로 제출함

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# ABSTRACT

**Objectives**: Intracranial arteriovenous malformations (AVMs) display venosinus signals on arterial spin labeling (ASL) due to the presence of arteriovenous shunting. Our aim was to quantitatively correlate venosinus signal intensity on ASL with digital subtraction angiography (DSA) in patients with intracranial AVMs.

**Materials and Methods**: Magnetic resonance (MR) imaging and DSA were obtained on the same day in 40 patients (25, previously untreated; 15, previously treated) with intracranial AVMs. Two reviewers assessed the ASL images based on identifying nidus, venous, and sinus signal intensities to determine the presence of arteriovenous shunting. Interobserver agreement on ASL between the reviewers was determined. The signal intensity measured from the veins or sinus on ASL was correlated with the time difference between normal and AVM venous transit times measured from the DSA images. Venosinus signal intensity was also correlated with AVM size.

**Results**: Interobserver agreement between the two reviewers for nidus, venous and sinus signal intensity was moderate-to-excellent ($\kappa$ = 0.44, 0.66, and 0.83, respectively). Interobserver agreement with respect to the presence of arteriovenous shunting was good ($\kappa$ = 0.79). Sinus signal intensity showed a positive relationship with the time difference between normal and AVM venous transit times ($P$ = 0.008). Sinus signal intensity also demonstrated a strong positive relationship with AVM size ($P$ < 0.0001).

**Conclusion**: Venosinus signal intensity on ASL is useful in identifying intracranial arteriovenous shunts. Sinus signal intensity measured on ASL correlates well with the degree of early vein opacification on DSA.

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**Keywords: Arteriovenous malformation (AVM), Arterial spin labeling (ASL), Venosinus signal intensity, Digital subtraction angiography (DSA)**

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# LIST OF TABLES AND FIGURES

# LIST OF ABBREVIATIONS

Arterial spin labeling (ASL)

Arteriovenous malformation (AVM)

Cerebral blood flow (CBF)

Digital subtraction angiography (DSA)

Gamma-knife surgery (GKS)

Middle cerebral artery (MCA)

Magnetic resonance (MR)

Intracranial hemorrhage (ICH)

Region of interest (ROI)

# Introduction

Intracranial arteriovenous malformations (AVMs) are cerebral vascular malformations characterized by the presence of direct arteriovenous shunting with no intervening capillary beds. They form an abnormal tangle of blood vessels, the so-called nidus, which is extremely fragile and at high risk for bleeding; in fact, 40-70% of patients with AVMs present with intracranial hemorrhages (ICHs), accounting for 2-4% of overall hemorrhagic strokes (1-4). Digital subtraction angiography (DSA) has long been the gold standard for the diagnosis of AVMs, because it clearly depicts angioarchitectural characteristics, such as the feeding artery, nidus and venous drainage.

The treatment options for intracranial AVMs include microsurgery, stereotactic radiosurgery and endovascular embolization (5). As the treatment often comprises multimodality and/or multistep procedures4 and it may take up to 4 or more years for AVMs to be obliterated after radiosurgery (6), many patients undergo frequent follow-up imaging studies, among which DSA is the mainstay. However, DSA is invasive and poses an inherent risk, although small (7). Therefore, a non-invasive imaging modality would be desirable for patients with AVMs in follow-up in particular.

Arterial spin labeling (ASL) is a relatively new magnetic resonance (MR) technique that utilizes water protons in the arterial water blood as endogenous tracers to assess cerebral blood flow (CBF) (8). Arterial blood protons labeled at the proximal portion to the brain with radiofrequency pulses readily diffuse into the brain tissue. Obtaining a signal at a certain time delay, in which most

labeled protons can be found in the capillaries, renders the tissue perfusion signal. Under the presence of arteriovenous shunting, arterial blood moves directly into the veins without passing the capillaries or brain tissue, where the labeled protons lose their signal because the T1 decay is shorter than the capillary transit time. Thus, this phenomenon contributes to the venous ASL signal intensity (9-11). Recently, Le et al (11) demonstrated that venous ASL signals improved the detection of small intracranial AVMs.

Because the signal intensity in a voxel on ASL is determined by the numbers of labeled protons in the corresponding area, we hypothesized that ASL signal intensity in the draining vein of an AVM may reflect the degree of the arteriovenous shunt. The purpose of this study was to correlate venous or sinus signal intensity measured on ASL with the DSA findings with respect to the degree of arteriovenous shunting in patients with intracranial AVMs.

# Materials and Methods

This study was approved by the institutional review board at our institution, and informed consent was waived. Demographic and radiographic data prospectively recorded in the database were retrospectively reviewed.

### *Patient Population*

From March 2011 through February 2012, 40 patients who had been planning to undergo gamma-knife surgery (GKS) for intracranial AVMs were enrolled in the study. Of these, 25 patients had received no prior treatment for AVM; 14 patients had previously undergone one or more session of GKS; and one patient had been previously treated with embolization using Onyx (ev3 Neurovascular, Irvine, CA). All 15 patients who received prior treatments had residual AVMs confirmed on the previous session of DSA.

### *Imaging Methods*

All patients underwent catheter-based DSA and brain MR imaging, including ASL, to localize the AVMs for GKS on the same day. The biplane angiography unit (Integris Allura systems; Philips Healthcare, Best, the Netherlands) was used for DSA examinations, which included antero-posterior and lateral projections with the selective injection of the appropriate internal carotid, external carotid and/or vertebral arteries with nonionic monomeric iodine contrast medium (Iopamidol, Pamiray 250, Dongkook Pharmaceutical, Seoul, Korea). MR imaging was performed on a 3 tesla MR

scanner (Verio; Siemens Medical Solutions, Erlangen, Germany) with a pre- and post-enhanced T1-weighted three-dimensional spoiled gradient echo sequence of 1.5-mm slice thickness and fast spin echo T2-weighted sequence of 1.5-mm slice thickness. Contrast enhancement was achieved with 0.1 mmol/kg gadobutol (Gadovist, Bayer Schering Pharmaceutical, Berlin, Germany).

The ASL perfusion imaging was performed using a pseudocontinuous ASL pulse sequence with a background-suppressed 3-dimensional gradient and a spin echo readout (labeling pulse duration = 1.5 seconds, post-labeling delay = 1.6 seconds, no flow crushing gradient, repetition time = 3660 milliseconds, echo time = 14.0 milliseconds, field of view = 24 × 24 $cm^2$, matrix = 64 x 64, slice thickness = 5 mm, 60 pairs of tags and controls acquired). The signal intensity change between the labeled image and the control image was fitted to a model, from which a quantitative perfusion map of CBF was obtained.

### *Image Analysis*

ASL images were independently reviewed by two reviewers (K.S.Y. and J.Y.L.) blinded to the patient histories and DSA findings. The reviewers determined the presence of venous or sinus ASL signal intensity. Nidus signal intensity was defined as a focal or serpiginous high signal intensity in the brain parenchyma. Venous signal intensity was defined as a serpiginous high signal intensity along the location of the cortical veins. Sinus signal intensity was defined as high signal intensity in the location of a major venous structure

(superior sagittal sinus, transverse sinus, sigmoid sinus, straight sinus, vein of Galen, internal cerebral vein). The reviewers then stated whether they thought arteriovenous shunting was present. After resolving cases with disagreements by discussion, the reviewers finally reached a consensus. Signal intensity in each venous and sinus signal intensity was measured within a region of interest (ROI) of approximately 3 $mm^2$ using a hot spot method.

The two reviews also analyzed the DSA images by consensus, in terms of Spetzler-Martin grade, arterial transit time, nidus opacification time, draining vein opacification time, and normal venous transit time. The time difference between AVM and normal venous transit time ($\Delta T_{AVM\text{-}normal}$, seconds) was calculated by subtracting the draining vein opacification time from the normal venous transit time in each patient.

### *Statistical Analysis*

To assess interobserver agreement for the evaluation of ASL images, we calculated the κ statistic for the two reviewers. Agreement between the reviewers was expressed as a κ value that accounted for the chance agreement between the two reviewers. κ values of less than 0 indicated a negative agreement; those of 0-0.20 indicated a positive but poor agreement; those of 0.21-0.40 indicated a fair agreement; those of 0.41-0.60 indicated a moderate agreement; those of 0.61-0.80 indicated a good agreement; and those of greater than 0.81 indicated an excellent agreement.

Using a Pearson's regression model, $\Delta T_{AVM\text{-}normal}$ and the size of the AVM were correlated with venous and sinus signal intensity after logarithmic transformation, respectively, as we assumed that these parameters did not exhibit linear relationships. Student's *t*-tests were performed to compare the mean values of the variables.

All statistical analyses were performed with MedCalc software (Version 13.1.1.0 for Microsoft Windows XP/Vista/7/8, MedCalc Software, Mariakerke, Belgium). The results with *P* values less than 0.05 were considered statistically significant.

# Results

### *Patient Demographics*

The mean age of the patients was 37.4 ± 15.1 years (range, 14 – 72 years). There were 17 females and 23 males in the subjects. The presenting symptoms of untreated patients were as follows: headache in eight patients, ICH in six patients, seizure in six patients, visual field defect in two patients, asymptomatic in two patients, and hemiparesis in one patient. The follow-up period for the GKS-treated patients ranged from 25 to 108 months (mean, 53.0 ± 26.8 months). Excluding two cases that showed complete obliteration of the nidus on DSA, the mean size of AVMs was 1.92 ± 0.86 cm (range, 0.73 – 5.0 cm).

### *Image Analysis*

The κ values of interobserver agreement between the two reviewers for ASL findings are shown in Table 1. The overall agreements on the presence of nidus, venous, and sinus signal intensity were moderate, good, and excellent, respectively. When these venosinus signals were taken into account simultaneously, the agreement for the presence of arteriovenous shunting was good.

Disagreement about the nidus signal was observed in eight patients (20.0%). Among these cases, the nidus signal was masked by a large high flow venous signal void in one case (Fig. 1), and by a magnetic susceptibility artifact in another patient who underwent embolization using Onyx (Fig. 2).

Disagreement about the venous and sinus signal intensity was noted in five (12.5%) and two (5%) cases, respectively. There was only one case with disagreement (2.5%) regarding the presence of arteriovenous shunting, which is described in Figure 3. After reaching a consensus, the two reviewers correctly identified arteriovenous shunts in all cases, considering DSA as the reference standard.

In the two cases with complete obliteration of the nidus, the reviewers agreed that there was no venosinus signal on ASL. In one of these two cases, the obliterated nidus showed focal contrast enhancement with surrounding T2 hyperintensity change, which was interpreted as a radiation-induced change (Fig. 4).

Venous and sinus signal intensity could be determined in 34 and 36 patients, respectively. There was no significant correlation between venous signal intensity and $\Delta T_{AVM\text{-}normal}$ ($P = 0.40$). However, sinus signal intensity showed a positive correlation with $\Delta T_{AVM\text{-}normal}$ (Fig. 5, $R^2 = 0.19$, $P = 0.0083$). Both venous and sinus signal intensity also exhibited a positive relationship with the size of the AVM ($R^2 = 0.26$, $P = 0.0022$; $R^2 = 0.42$, $P < 0.0001$, respectively). The mean $\Delta T_{AVM\text{-}normal}$ in the treated group was significantly shorter than that in the untreated group ($3.02 \pm 1.00$ vs. $3.74 \pm 0.72$, $P = 0.017$). In the untreated group, sinus signal intensity was significantly lower in patients who presented with hemorrhage, compared to those who presented with symptoms other than hemorrhage or who were asymptomatic ($P = 0.0007$).

| | $\kappa$ | 95% CI |
|---|---|---|
| Nidus signal intensity | 0.44 | 0.14-0.75 |
| Venous signal intensity | 0.66 | 0.39-0.93 |
| Sinus signal intensity | 0.83 | 0.59-1.00 |
| Arteriovenous shunting | 0.79 | 0.39-1.00 |

**Table 1. Interobserver agreement on the ASL findings between the two reviewers.** ASL = arterial spin labeling

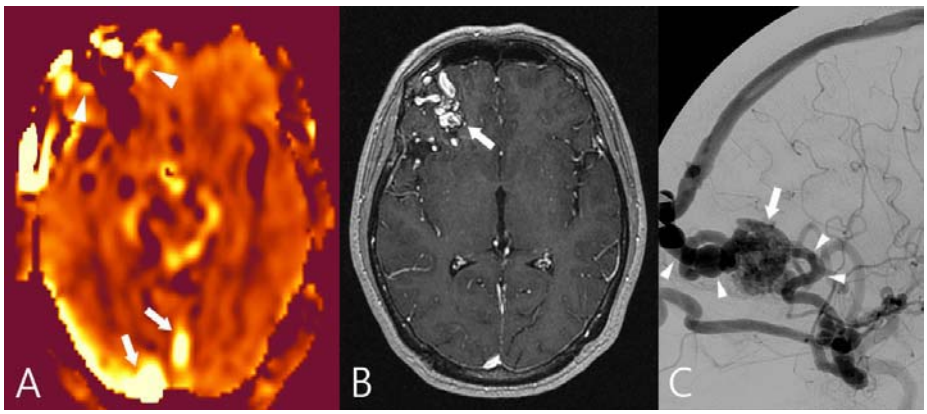


**Figure 1. A 52-year-old female who presented with headache.** (A) Axial arterial spin labeling (ASL) image shows multiple high signal intensity foci (arrowheads) adjacent to large signal void area in the right frontal lobe. One of the reviewers regarded these hyperintense foci as negative because he thought they were symmetric to the signal in the contralateral frontal lobe. The image also shows intense signal intensity in the right transverse sinus and straight sinus (arrows). After discussion, the reviewers agreed that the high signal foci in the right frontal lobe represents a nidus signal. (B) Axial T1-weighted post-contrast image shows multiple tubular enhancing structures in the right frontal lobe (arrow). They represent a nidus with dilated veins. (C) Lateral digital subtraction angiography (DSA) confirms a frontal arteriovenous malformation (AVM, arrow) fed by frontopolar arteries originating from the right middle cerebral artery (MCA), with dilated venous structures (arrowheads) draining into the superior sagittal sinus and cavernous sinus.

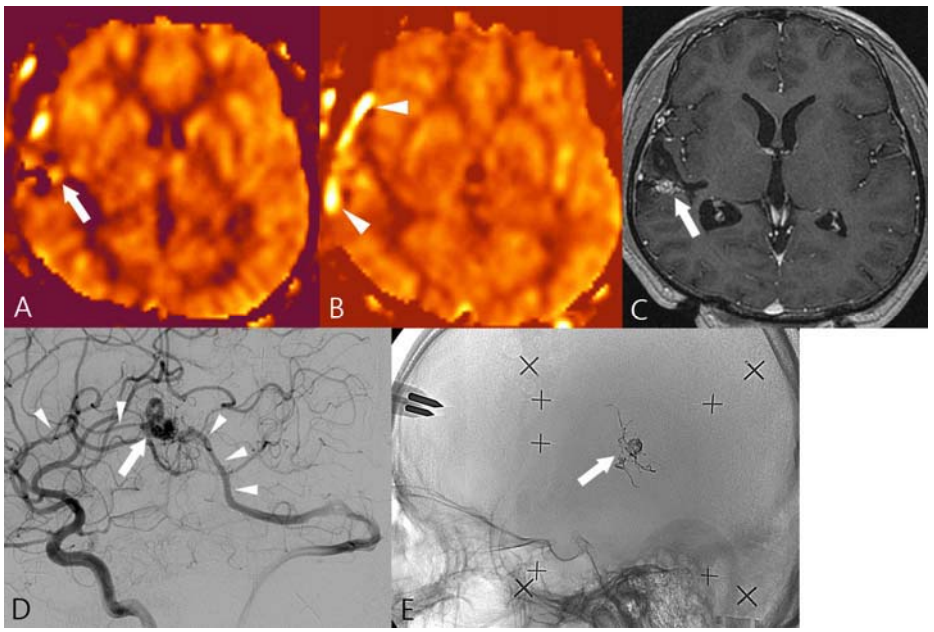


**Figure 2. A 30-year-old male with left homonymous hemianopsia.** (A and B) Axial ASL images. There is a tiny asymmetric high signal intensity adjacent to the signal void area in the right temporal lobe (A, arrow). One of the reviewers overlooked this intensity but detected a serpiginous high signal intensity along the location of cortical vein in the right temporal lobe (B, arrowheads), which he determined was a venous signal. After discussion, the two reviewers concluded that the high signal intensity in the right frontal lobe (A) represented a nidus signal. (C) Axial T1-weighted post-contrast image shows a small enhancing vascular lesion (arrow) in the right temporal lobe. (D) Lateral DSA confirms a temporal AVM (arrow) fed by multiple feeders originating from the right MCA and engorged veins (arrowheads) draining into the sphenoparietal and transverse sinus. E, Lateral plain radiograph shows a radiopaque cast in the corresponding area (arrow). The patient had previously undergone endovascular embolization using Onyx (not shown).

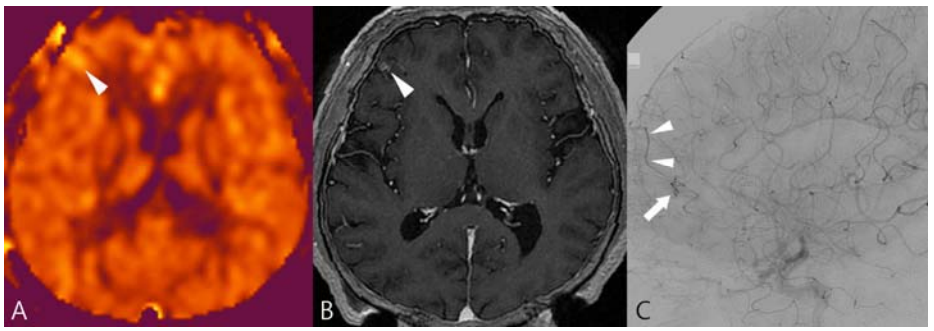


**Figure 3. A 54-year-old male who underwent gamma-knife surgery for the right frontal AVM 37 months ago.** (A) Axial ASL image shows a slightly high signal intensity in the right frontal lobe (arrowhead). No venosinus signal intensity is clearly demonstrated. Initially, there was disagreement between the reviewers as to whether this intensity corresponded to a nidus. After discussion, the reviewers decided that this asymmetric high signal intensity represented a nidus. (B) Axial T1-weighted post-contrast image shows a small enhancing lesion (arrowhead) in the right frontal lobe. (C) Lateral DSA confirmed a very small nidus (arrow) and cortical vein (arrowheads) draining into the superior sagittal sinus.

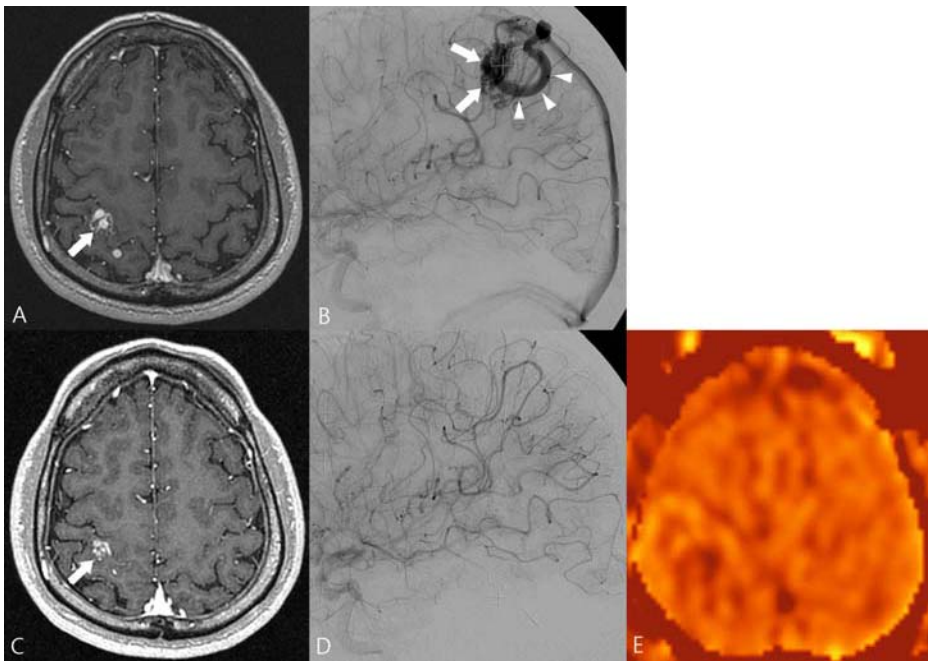


**Figure 4. A 28-year-old male who underwent GKS for a right parietal AVM.** (A-B) Axial T1-weighted post-contrast image (A) and DSA (B) performed 38 months after initial GKS as a GKS-planning study. (A) A few enhancing tubular structures (arrow) indicate residual AVM at the right parietal lobe. (B) Lateral DSA confirmed a residual AVM (arrows) supplied by the right MCA and cortical vein (arrowheads) draining into the superior sagittal sinus. (C-E) Axial T1-weighted post-contrast image (C), DSA (D), and axial ASL image (E) performed 88 months after initial GKS and 50 months after second GKS. (C) Remaining clustered enhancing foci at the right parietal lobe gave rise to the suspicion of residual nidus. (D) However, the AVM was completely obliterated without demonstrable nidus on DSA. (E) On ASL, no abnormal venosinus signal intensity was noted in the corresponding area.

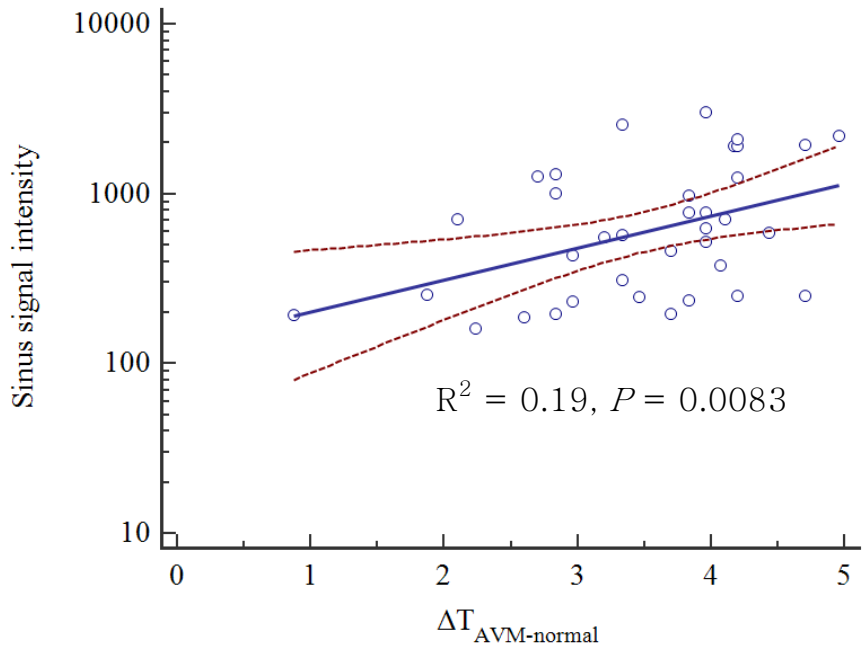


**Figure 5. Correlation of sinus signal intensity and time difference between AVM draining vein opacification and normal vein opacification ($\Delta T_{AVM\text{-}normal}$).** Logarithmic transformations were applied to the sinus signal intensity. Dashed lines indicate the 95% confidence interval.

# Discussion

In the present study, we have shown that interobserver agreement on the presence of a venosinus signal was excellent. Overall agreement for the presence of an arteriovenous shunting was good. In addition, we have demonstrated that the signal intensity measured from the draining sinus of an AVM on ASL correlated well with the time difference between the normal vein opacification and AVM draining vein opacification and with the AVM size.

Because there is no signal in the veins on ASL under normal conditions, venous and sinus ASL signal intensity is a robust sign of the presence of an arteriovenous shunt (9-11). In this study, venosinus signal intensity proved useful in detecting arteriovenous shunt in patients with intracranial AVMs. The nidus of an AVM could also be reproducibly identified in many cases by carefully tracing the venous and/or sinus signal to the upstream (Fig. 2). These findings suggest that ASL is applicable to the evaluation of small-sized AVMs with relatively slow shunts.

The intensity of the venous signal on ASL in a patient with an AVM stands for the numbers of labeled protons in the veins, which is related to the degree of shunt. The higher the shunt rate is, the sooner the draining vein should be opacified. Therefore, we assumed that the degree of shunting on DSA could be expressed as the difference between the time of AVM draining vein opacification and the time at which the normal veins are opacified ($\Delta T_{AVM-normal}$). Sinus signal intensity showed a significant correlation with $\Delta T_{AVM-normal}$,

in line with our hypothesis. The correlation coefficient and the level of statistical significance were higher after applying logarithmic transformations to the sinus signal intensity, indicating that there is a possible exponential relationship between these two variables. Venous signal intensity failed to exhibit a significant correlation with $\Delta T_{AVM\text{-}normal}$, probably because the signal was relatively small and heterogeneous.

According to Spetzler et al (12), the major factors determining the difficulty of AVM operation include size, number of feeding artery, amount of shunt flow, location, eloquence of neighboring brain, and venous drainage pattern. By simplifying these factors to three variables (size, eloquence of adjacent brain, and venous drainage), they proposed a grading system, namely the Spetzler-Martin grade, which is widely used in clinical practice to predict the surgical outcomes of patients with intracranial AVMs (13). The amount of shunt flow is important in describing the steal phenomenon (14-18), which occurs as a result of blood flow deprivation in the adjacent brain tissue by a low-pressure system in an AVM. Certain previous reports (16, 18, 19) proposed that the presence of a cerebral steal may be a protective factor for hemorrhage. In our study, we also found that previously untreated patients who presented with hemorrhage showed significantly lower sinus signal intensity than those who presented with symptoms other than hemorrhage or were asymptomatic.

Radiation-induced changes following GKS include vascular damages with blood-brain barrier breakdown, ischemia, vasogenic edema, demyelination,

and radiation necrosis (20, 21). Abnormal enhancement was observed in 60% of the patients with obliterated AVMs in a report (20). In our study, there was one such case, which did not show any venosinus signal intensity on ASL (Fig. 4). This finding suggests venosinus signal intensity on ASL may help differentiating radiation-induced change from residual arteriovenous shunting.

ASL has been recently drawing increased interest from clinicians and radiologists due to its capacity to quantify absolute CBF data without using a contrast medium. As such, ASL can be conveniently performed and reliably evaluated in a patient who requires repeated follow-up imaging studies. One limitation of ASL is its susceptibility to the magnetic field distortion caused by neurosurgical hardware, calcification, blood products and air, any of which can lead to a decreased signal intensity (22). A high shunt flow also produces signal loss and may hinder the interpretation of nidus signal intensity. Under these circumstances, recognizing abnormal signals in the sinus becomes particularly helpful for detecting abnormal arteriovenous shunting (Fig. 1).

Aside from the retrospective design, there are a few limitations in this study. First, the sample size was relatively small, and there was no follow-up study in each patient. In addition, the case number of negative control group are too small compared to that of the study group. Second, we did not perform comparison studies with conventional imaging findings to seek for the added values of venosinus signal intensity on ASL in the diagnosis of AVM. Third, we used a fixed post-labeling delay time without changing this value from the routine imaging studies. Because the rate of shunt differs among the patients,

there could be unknown bias in our results, although we believe such a value would be small. Considering that ASL is free from issues pertaining to radiation and contrast injection, the performance of a prospective study design that includes negative controls with follow-up imaging studies would be desirable.

# Conclusions

Venosinus ASL signal intensity can help determining the presence of arteriovenous shunting reproducibly. Sinus signal intensity correlates well with the degree of early vein opacification on DSA, which in turn corresponds to the degree of shunting.

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# 국문 초록

**목적:** 두개강내 동정맥 기형은 동맥스핀라벨링 기법을 이용한 자기공명영상에서 동정맥 단락에 의한 정맥동 신호강도를 나타낸다. 본 연구는 두개강내 동정맥 기형 환자의 동맥스핀라벨링 영상에서 보이는 정맥동 신호강도를 감산혈관조영술 소견과 비교하여 준정략적으로 분석하였다.

**대상 및 방법:** 총 40 명의 두개강내 동정맥 기형 환자 (이전 치료력 없는 환자, 25 명; 치료력 있는 환자, 15 명)에서 같은 날 자기공명영상과 감산혈관조영술을 시행하였다. 두 명의 영상의학과 의사가 각각 동맥스핀라벨링 영상에서 각각 병소, 정맥, 그리고 정맥동 신호강도가 보이는지의 여부에 기초하여 동정맥 단락의 유무를 개별적으로 판정하였고, 이를 토대로 관찰자간 일치도를 계산하였다. 또한 감산혈관조영술에서 측정한 정상정맥 조영시간과 동정맥 기형의 유출정맥이 조영되는 시간의 차를 계산하여, 이를 동맥스핀라벨링 영상에서 측정한 정맥 혹은 정맥동 신호강도와 각각 상관분석을 시행하였다. 마찬가지로, 정맥동 신호강도와 동정맥 기형의 크기에 대해서도 상관분석을 시행하였다.

**결과:** 병소, 정맥, 그리고 정맥동 신호강도 각각에 대한 관찰자간 일치도는 각각 중등도, 우수, 매우 우수에 해당했다 (각각 $\kappa$ = 0.44, 0.66, 그리고 0.83). 동정맥 단락의 유무에 대한 관찰자간 일치도는 우수하였다 ($\kappa$ = 0.79). 정맥동 신호강도는 정상 및 동정맥 기형 정맥유출 시간의 차와 유의한 양의 상관관계를 보였다 ($P$ = 0.008). 정맥동 신호강도는 동정맥 기형의 크기에 대해서도 강한 양의 상관관계를 보였다 ($P < 0.0001$).

**결론:** 동맥스핀라벨링 영상에서 보이는 정맥동 신호강도는 두개강내 동정맥 단락을 발견하는데 유용하다. 정맥동 신호강도는 감산혈관조영술에서 측정한 조기 정맥 유출의 정도와 좋은 상관관계를 나타낸다.

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**주요어: 동정맥 기형, 동맥스핀라벨링, 정맥동 신호강도, 감산혈관조영술**

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