Underestimation of Cerebral Perfusion on Flow-Sensitive Alternating Inversion Recovery Image: Semiquantitative Evaluation with Time-to-Peak Values

BACKGROUND AND PURPOSE: We assessed the underestimation of cerebral perfusion measured by the flow-sensitive alternating inversion recovery (FAIR) technique in patients with carotid stenosis and compared the technique with dynamic susceptibility contrast (DSC) MR images.

MATERIALS AND METHODS: We studied 42 areas of decreased cerebral blood flow (CBF) using 3 FAIR images with different inversion times (TIs) in 42 consecutive patients with unilateral carotid stenosis of more than 50%. The width of decreased CBF area (wCBF) was qualitatively assessed. We analyzed the ratio of CBF (rCBF) and the time-to-peak (TTP) difference (dTTP) between the ipsilateral hemisphere to carotid stenosis and contralateral normal area using regions of interest (ROIs) at the same location.

RESULTS: In the areas with more prolonged TTP (dTTP ≥3.2 s), the wCBF obtained from the FAIR images with TI of 1600 ms was smaller than those from the FAIR images with a TI of 800 ms and 1200 ms in all cases. The mean rCBF obtained from the FAIR images with a TI of 1200 ms was significantly lower than that obtained from the FAIR images with a TI of 1600 ms (P < .01) in the areas with more prolonged TTP. In the areas with less prolonged TTP (dTTP <3.2 s), the wCBF and mean rCBF were not significantly different between the 2 FAIR images (TI, 1200 and 1600 ms).

CONCLUSION: If TTP is delayed significantly (dTTP ≥3.2 s), the FAIR with intermediate or short TI showed underestimation of perfusion in the same area with delay in TTP.

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From the Department of Diagnostic Radiology, Ajou University, College of Medicine, Kyunggi-do, Republic of Korea.

Please address correspondence to Ho Sung Kim, MD, Department of Diagnostic Radiology, Ajou University, School of Medicine, Mt. 5, Woncheon-dong Yeongtong-gu, Suwon-si, Gyeonggi-do 442-749, Republic of Korea; e-mail: J978005@lycos.co.kr

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Materials and Methods

Patients

Between May 2005 and March 2006, 42 consecutive patients (mean age, 57 years; age range, 15–80 years; 22 male, 20 female) with unilateral carotid stenosis underwent pulsed ASL MR imaging with the
FAIR technique, as well as DSC MR images. We evaluated 42 areas of decreased CBF in these patients. To determine the degree of stenosis of the internal carotid artery (ICA), we used the criteria of the North American Symptomatic Carotid Endarterectomy Trial (NASCET).14 We evaluated stenosis of the ICA with CT angiograms \( (n = 42) \) and conventional digital subtraction angiograms \( (n = 25) \). In all cases with ICA stenosis, the degree of stenosis of the ipsilateral ICA was greater than 50% (50% to 70%, 35 patients; 70% to 90%, 7 patients), and the contralateral ICA was normal. ICA stenosis was found at the origin of the ICA around the carotid bifurcation in 32 patients and at the distal supraclinoid ICA in 10 patients. No patients had a major stroke, and none were thrombolytic candidates. The patients had experienced single or recurrent episodes of a transient ischemic attack \( (n = 19) \) or a minor stroke \( (n = 5) \). Transient neurologic deficits were defined as symptoms that lasted for less than 24 hours. A minor disabling deficit was associated with a Rankin scale score (defined as symptoms that persisted for longer than 24 hours).15 We obtained informed consent from all patients and their relatives, and the institutional review board of our hospital approved the study protocol.

**MR Imaging Protocol**

We performed MR images with a 1.5T system (Signa Excite; GE Healthcare, Milwaukee, Wis) and included the following sequences: axial fast spin-echo T2-weighted imaging, axial spin-echo T1-weighted imaging, fluid-attenuated inversion recovery imaging, diffusion-weighted imaging, FAIR imaging, and DSC MR imaging. An 8-channel head coil was used for radio-frequency transmission and signal intensity reception during all MR images.

The FAIR sequence comprised alternating section-selective and nonselective radio-frequency inversion pulses and was performed with TIs of 800, 1200, and 1600 ms between the labeling and image acquisitions. This range of TIs \( (800–1600\) ms) was selected on the basis of the TI decay of magnetically labeled water.16 We obtained the final FAIR maps by subtracting the nonselective inversion recovery images from the section selective images at each of the 3 different TIs. Other imaging parameters used to perform the multisection FAIR technique were TR, 2000 ms; TE, 15 ms; FOV, 24 cm; matrix, \( 128 \times 128 \); NEX, 100; section thickness, 5 mm; number of sections, 7; and section gap, 2 mm. The total acquisition time for FAIR imaging was 3 minutes, 22 seconds. Seven FAIR image sections were acquired at the same locations as the DSC MR images.

The DSC MR images were performed with gradient-echo echo-planar sequences during the injection of 0.2 mmol/kg of body weight gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) at a rate of 4 mL/s with an MR-compatible power injector (Spectris; MedRad, Indianola, Pa). The bolus of contrast material was followed by a 15-mL bolus of saline that was administered at the same injection rate. A gradient-echo echo-planar sequence was used with the following parameters: TR, 1600 ms; TE, 80 ms; flip angle, 90°; FOV, 24 cm; matrix, \( 128 \times 128 \); section thickness, 5 mm; number of sections, 7; and section gap, 2 mm. All images were transferred to a workstation (Advantage Workstation 4.1, GE Healthcare). Perfusion maps of relative cerebral blood volume (wCBF) ipsilateral to the carotid stenosis on each of the 3 FAIR images were evaluated the width of the area in which the CBF was diminished (wCBF) ipsilateral to the carotid stenosis on each of the 3 FAIR images.

Images were analyzed prospectively by 2 neuroradiologists who were blinded to the clinical data of the patients and to the findings obtained with the other imaging technique. The neuroradiologists qualitatively evaluated the width of the area in which the CBF was diminished (wCBF) ipsilateral to the carotid stenosis on each of the 3 FAIR images. To compare the wCBFs between the 3 FAIR images, the 2 observers examined the images together and reached a final decision that was consensual. Each wCBF region obtained with a TI of 800 was categorized as being greater than, less than, or equal to the corresponding wCBF region with TIs of 1200 and 1600. The wCBF region obtained with a TI of 1200 was also categorized as being greater than, less than, or equal to the corresponding wCBF region with a TI of 1600.

To analyze the regions of interest (ROIs), we spatially coregistered all pulsed arterial spin-labeling (PASL) images to the DSC MR images to superimpose the ROIs delineated on the TTP map with use of SPM2 software (Wellcome Department of Cognitive Neuroscience, London, England). All PASL and DSC MR images were coregistered into the volume data with the same \( 128 \times 128 \) matrix. After selection of patients with delay in TTP, the 2 observers consensually identified the most prolonged area of TTP and independently drew a ROI in the visually most prolonged area of TTP ipsilateral to the carotid stenosis. These ROIs were transferred to the corresponding coregistered PASL images. Each ROI value on the TTP and 3 FAIR images was averaged from the measurements obtained by the 2 observers. For comparison, mirror ROIs were manually redrawn on the TTP maps for the contralateral hemisphere. The relative ratio of CBF (rCBF) on the PASL images was calculated by dividing the lesion values by the mirror ROI value of the contralateral hemisphere. Delay in TTP was defined as the difference between the TTP (dTTP) of a lesion and that of the contralateral hemisphere. The size of each ROI was 300 mm\(^2\). We defined the cutoff value of dTTP as the minimum value that produced a significant difference in rCBF between the FAIR image with the longest TI (1600 ms) and that with the intermediate TI (1200 ms). Differences in wCBF and rCBF between the 3 FAIR images were analyzed according to the dTTP cutoff value.

**Statistical Analysis**

The rCBF data obtained by the 3 FAIR images were pooled according to the values of dTTP. Pearson correlation coefficients of rCBF values between the 3 FAIR images were calculated according to the cutoff value of the dTTP. Repeated measures analysis of variance (ANOVA) was used to test for a statistically significant difference of the rCBF among the 3 FAIR images according to the cutoff value of the dTTP. If a significant difference was found, the Tukey-Kramer multiple comparisons test was used for post hoc analysis. A \( P \) value < .05 was considered to indicate a statistically significant difference.

**Results**

The T2-weighted images revealed multiple small areas of high signal intensity predominantly within the affected centrum semiovale and corona radiata in 7 patients. None of the patients exhibited evidence of territorial infarcts. The areas
where the CBF was diminished and the TTP was prolonged included the external watershed areas between the middle cerebral artery (MCA) and the anterior or posterior cerebral artery territories, the internal watershed areas, and the ipsilateral MCA territories.

The wCBF obtained from the FAIR images was smaller than that of the TTP map (Table 1). The mean dTTP of all patients was 3.0 s (range, 0.8–8.0 s). The cutoff value of the dTTP that produced a significant difference in rCBF between the FAIR image with the longest TI (1600 ms) and that with the intermediate TI (1200 ms) was 3.2 s. Among the 42 areas of decreased CBF, the dTTP was more than 3.2 s in 17 areas and dTTP was less than 3.2 s in 25 areas.

The wCBFs obtained from each of the 2 FAIR images with TIs of 800 ms and 1200 ms were larger than that obtained from the corresponding FAIR image with a TI of 1600 ms in the 12 of 17 areas with a more prolonged TTP (dTTP ≥ 3.2 s) (Fig 1), and in the 3 of 25 areas with a less prolonged TTP (dTTP < 3.2 s).

Correlations of the rCBF values obtained from each of the 3 FAIR images were stronger in the areas with a less prolonged TTP (dTTP < 3.2 s) than in the areas with a more prolonged TTP (dTTP ≥ 3.2 s) (Table 2).

In the areas where the TTP was less prolonged (dTTP < 3.2 s), the mean rCBF values obtained from the FAIR image with a TI of 800 ms were significantly lower than those obtained from each of the 2 FAIR images with a TIs of 1200 and 1600 ms (P < .01). However, there were no significant differences be-

### Table 1: Width of decreased CBFs among the three FAIR maps with different inversion times according to the TTP difference

| wCBF | dTTP < 3.2 s (%) | dTTP ≥ 3.2 s (%) |
|------|-----------------|-----------------|
| FAIR 800 < FAIR 1200 | 0/25 (0) | 0/17 (0) |
| FAIR 800 = FAIR 1200 | 23/25 (92) | 12/17 (71) |
| FAIR 800 > FAIR 1200 | 2/25 (8) | 5/17 (29) |
| FAIR 800 < FAIR 1600 | 0/25 (0) | 0/17 (0) |
| FAIR 800 = FAIR 1600 | 17/25 (68) | 3/17 (18) |
| FAIR 800 > FAIR 1600 | 8/25 (32) | 14/17 (82) |
| FAIR 1200 < FAIR 1600 | 0/25 (0) | 0/17 (0) |
| FAIR 1200 = FAIR 1600 | 22/25 (88) | 5/17 (29) |
| FAIR 1200 > FAIR 1600 | 3/25 (12) | 12/17 (71) |

**Note:** wCBF, width of decreased CBF; dTTP, TTP difference; FAIR 800, TI = 800 ms; FAIR 1200, TI = 1200 ms; FAIR 1600, TI = 1600 ms.

### Table 2: Correlation coefficients of rCBF among the three FAIR maps

| Groups | dTTP < 3.2 s | dTTP ≥ 3.2 s |
|--------|-------------|-------------|
| FAIR 800 vs FAIR 1200 | r = 0.764, P < .01 | r = 0.712, P < .01 |
| FAIR 800 vs FAIR 1600 | r = 0.667, P < .01 | r = 0.595, P < .01 |
| FAIR 1200 vs FAIR 1600 | r = 0.791, P < .01 | r = 0.612, P < .01 |

**Note:** dTTP indicates TTP difference; FAIR 800, TI = 800 ms; FAIR 1200, TI = 1200 ms; FAIR 1600, TI = 1600 ms; r, correlation coefficient.
Table 3: Comparison of rCBF among the three FAIR images in the areas with less prolonged TTP (dTTP <3.2 s)*

| Comparison           | MD     | P Value | 95% CI          |
|----------------------|--------|---------|-----------------|
| FAIR 800 vs FAIR 1200| -0.031 | <.05    | -0.086–0.003    |
| FAIR 800 vs FAIR 1600| -0.046 | <.001   | -0.075–0.017    |
| FAIR 1200 vs FAIR 1600| -0.015 | >.05    | -0.043–0.014    |

Note:—MD indicates mean difference; CI, confidence interval; FAIR 800, TI = 800 ms; FAIR 1200, TI = 1200 ms; FAIR 1600, TI = 1600 ms.

* Statistical analysis was performed with the repeated measures ANOVA and post hoc analysis with the Tukey-Kramer multiple comparisons test.

Table 4: Comparison of rCBF among the three FAIR images in the area with more prolonged TTP (dTTP ≥3.2 s)*

| Comparison           | MD     | P Value | 95% CI          |
|----------------------|--------|---------|-----------------|
| FAIR 800 vs FAIR 1200| -0.026 | <.05    | -0.049–0.002    |
| FAIR 800 vs FAIR 1600| -0.078 | <.001   | -0.101–0.054    |
| FAIR 1200 vs FAIR 1600| -0.052 | <.001   | -0.075–0.029    |

Note:—MD indicates mean difference; CI, confidence interval; FAIR 800, TI = 800 ms; FAIR 1200, TI = 1200 ms; FAIR 1600, TI = 1600 ms.

* Statistical analysis was performed with the repeated measures ANOVA and post hoc analysis with the Tukey-Kramer multiple comparisons test.

being used to examine patients with ischemic cerebrovascular disease.\textsuperscript{20–21} Compared with continuous ASL (CASL), which uses relatively long width radio-frequency (RF) pulses, PASL techniques use nearly instant pulses with comparatively low levels of RF deposition for spin labeling and are particularly advantageous in circumstances in which the specific absorption rate (SAR) imposes a limitation, such as a high magnetic field and pediatric imaging.\textsuperscript{22} However, the short half-life of spin-labeled arterial water can complicate the quantification of perfusion on PASL. Labeling must be followed by a delay period (the TI) before PASL MR images are acquired. The loss of contrast as a result of TI relaxation during transit delay from the labeling site to the tissue of interest can result in an underestimation of CBF unless this delay is taken into account; such underestimation of CBF is more pronounced for brain regions in which perfusion is significantly delayed.\textsuperscript{6,7}

An ideal inversion time for PASL yields high tissue signal intensity and minimal intravascular signal intensity. By varying the TI in our patients with unilateral carotid stenosis, we noticed that the perfusion signal intensity was very dependent on the chosen TI, with a decreasing area of perfusion defect at higher values of TI. In the normal hemisphere, the perfusion signal intensity ratio peaks when TI is approximately 1200 ms; however, in the affected hemisphere ipsilateral to the carotid stenosis, the maximum perfusion signal intensity ratio occurs when TI reaches 1600 ms.

The transit delay is related to the fundamental problem that the time required for tagged arterial blood to travel from the tagging region to the capillary is similar to the TI of blood. This makes it necessary to acquire the image while many dynamic processes are taking place (delivery, exchange, clearance by TI and flow). If images are acquired too early after application of the tag, then CBF can be underestimated because of the presence of the transit delay.\textsuperscript{9} Quantitative imaging of perfusion with a single subtraction-second version (QUIPSS II)\textsuperscript{23} is a modification of the basic PASL technique

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that can be made insensitive to these sources of error in a
dynamic measurement. For applications in pathologic condi-
tions such as stroke or the presence of brain tumors, it is par-
ticularly important to use techniques that are insensitive to
large variations in transit delay. Wong et al19 have determined
experimentally that transit delay ranges from about 500 to
1500 ms for a physical gap of 1 to 3 cm between the tag region
and the imaging section.

In our study, the 3 FAIR images revealed differences in
perfusion according to the values of dTTP. The values of rCBF
obtained from the 2 FAIR images with a TI of 800 and 1200 ms
were significantly lower than those obtained from the corre-
sponding FAIR images with a TI of 1600 ms in the area with
more prolonged TTP (dTTP ≥3.2 s). According to our results
of the FAIR imaging study, long TIs should be used to evaluate
slow CBF in patients with carotid stenosis. Although this rec-
ommendation seems to be reasonable, it must be made with
some caution because there are limitations of the current com-
parison with DSC MR imaging, and no reliable standard ref-
ence is used.

Arbab et al21 reported a correlation between the single-
section FAIR perfusion images and contrast-enhanced dy-
namic perfusion MR images and found a good correlation
between FAIR and relative CBF. In our study, we used the TTP
method to quantify the blood flow transit delay and to assess
errors in CBF measurement from PASL imaging. TTP is a
simple measure of perfusion that calculates the time it takes
for the bolus of contrast to reach its maximum concentration
in a given region of the brain.24,25 This technique was shown to
be highly vulnerable to steno-occlusive disease and can be
concluded to be less reliable in the presence of steno-occlusive
vascular disease. However, this simple parameter is straight-
forward to compute and thus has become widely popular in
clinical practice. Moreover, some of the methods of deconvo-
lation were also vulnerable to the presence of steno-occlusive
disease, which may have been caused by the misrepresentation
of the selected arterial input function (AIF) for the flow at the
affected area of the brain.

Although it is ideal to analyze each pixel with the AIF of its
own feeding artery, this is not clinically feasible because a large
number of AIFs will be required. Thus, an AIF is typically chosen
from a single location, such as the ICA or MCA con-
tralateral to the side of the infarct.3,26,27 However, in the evalua-
tion of a patient with steno-occlusive disease, the AIF chosen
from the contralateral vessel may not represent the AIF of the
ipsilateral hemisphere, where there may be significant distor-
tion of the curve. The resultant mean transit time (MTT) im-
ages will tend to overestimate the region of abnormal flow,
resulting in lower specificity. Conversely, when the AIF is cho-
sen from the peri-infarct arteries, higher specificity to the local
flow disturbances is obtained, because the AIF corrects for the
contrast delay and dispersion that occur distal to the vascular
stenosis.

In our study, the reproducibility for selection of the AIF
from the artery from the affected side, including the peri-in-
farct artery, between the 2 observers was not high. Therefore,
we finally decided to use the TTP map as a comparative transit
time parameter, and the use of the TTP method as an indicator
of transit delay was a limitation of our study. However, we did
not consider the TTP map as the criterion standard for transit
time but simply compared the PASL with the TTP commonly
used perfusion parameter of a DSC MR image. Only a few of
our patients had a severe degree (>70%) of stenosis, which
could affect the determination of the TTP by a delay and dis-
persion.28 Second, we used multisection FAIR images in our
study. In a multisection application, increased transit delays to
the more distal sections is more prevalent than in a single-
section ASL because the transit delay between the tagging re-
gion and the more distal sections can be long. Another com-
pliation that accompanies multisection ASL is the consistency of
the static tissue signal intensity between the tag and
control states. Because the perfusion signal intensity is
small (<1%), it is critical that the subtraction of static tissue
signal intensity between the tag and control states be accurate.
In both CASL and PASL, only 1 section location receives ex-
actly the same radio-frequency radiation in the tag and control
states. Third, the relatively low signal-to-noise ratio of FAIR
images means that there is high variability among different
observers with respect to their analysis of ROI. In our study,
we reduced this variability by acquiring the 3 FAIR images at
the same locations where the DSC MR image was acquired and
by using the same size ROI in each image. Finally, the relatively
small sample size may have reduced the probability of detect-
ing a statistically significant relationship between the values
of rCBF obtained by using the 3 different FAIR images with dif-
ferent TIs.

Attempting to use the same TI in both the healthy control
and carotid stenosis groups was not ideal. Inversion timings in
PASL must be optimized to receive maximum perfusion-
weighted tissue signal intensity, and these times may differ
between the healthy controls and patients with carotid
stenosis.

Conclusion
A FAIR with an intermediate or short TI underestimates the
perfusion in the area of significant TTP delay (dTTP ≥3.2 s).
Therefore, TI optimization of a FAIR protocol should be con-
sidered for perfusion studies in patients with carotid stenosis.

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