Influence of Arterial Input Function on Hypoperfusion Volumes Measured With Perfusion-Weighted Imaging

Vincent N. Thijs, MD; Diederik M. Somford, MD; Roland Bammer, PhD; Wim Robberecht, MD, PhD; Michael E. Moseley, PhD; Gregory W. Albers, MD

Background and Purpose—The arterial input function (AIF) is critical in determining hemodynamic parameters quantitatively with bolus-tracking MRI. We studied the effect of varying the location of measurement of AIF on the volume of hypoperfusion. We compared the volumes of hypoperfusion obtained with different AIFs with the final ischemic lesion volume.

Methods—We included 13 patients with acute cerebral ischemia in the anterior circulation who underwent diffusion-weighted (DWI) and perfusion (PWI)-weighted imaging within 8 hours after symptom onset and exhibited DWI lesion expansion between baseline and follow-up. AIF was measured at 4 locations: near both middle cerebral arteries (MCAs), in MCA branches adjacent to the largest DWI abnormality, and at the same level on the opposite hemisphere. Hypoperfusion lesion volumes were compared with the DWI volume at follow-up.

Results—Large variations in PWI lesion size were found with different AIF locations. The largest PWI lesions were found when AIF was measured at the contralateral MCA. Smaller PWI lesions were found when AIF was measured in the other locations. There was no significant difference between PWI lesion area at baseline and follow-up DWI lesion when AIF was measured at the contralateral MCA. The other PWI lesions significantly underestimated follow-up DWI lesion size.

Conclusions—AIF is an important determinant of the size of hypoperfusion lesions measured with PWI. PWI lesion volumes determined with AIF from the contralateral MCA are associated with follow-up lesion volume. (Stroke. 2004;35:94-98.)

Key Words: magnetic resonance imaging, diffusion-weighted • magnetic resonance imaging, perfusion-weighted • stroke, acute • stroke, ischemic

Dynamic susceptibility contract-enhanced MRI is increasingly used to measure cerebral hemodynamic parameters in acute stroke patients. In combination with diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI) provides a powerful tool to identify tissue that might be rescued by acute intervention. Several shortcomings have been identified with the quantification of the dynamic susceptibility contract-enhanced MRI technique, including problems with measurement of the arterial input function (AIF) and with identification of tissue characteristics like hematocrit and brain density that are required to measure cerebral blood flow (CBF) accurately.

The function describing the concentration of gadolinium contrast agent over time as it enters the brain, called the AIF, is critical in determining hemodynamic parameters quantitatively with bolus-tracking MRI. The ideal location to determine AIF remains controversial. Partial volume artifacts might bias the results of AIF measurements in small vessels. On the other hand, AIF should be measured as close as possible to the tissue of interest to minimize delay and dispersion of the bolus between the area of measurement and the tissue of interest. It is also unclear whether AIF should be measured in the hemisphere ipsilateral to or opposite the hypoperfusion lesion.

We studied the effect of varying the location of measurement of AIF on the obtained volume of hypoperfusion. We compared the volumes of hypoperfusion obtained with different AIFs with the final DWI lesion volume and assessed whether AIF could be measured reliably by different observers.

Methods

Patients
We identified patients with acute nonlacunar ischemic stroke entered into the Stanford Stroke Center Database in whom an MRI with DWI and PWI was obtained within 8 hours of symptom onset and 4 to 7 days after symptom onset. This later period was chosen because previous studies indicate that DWI lesion volume growth is complete by 4 to 7 days. Eligible patients were required to have an acute DWI lesion volume that increased in volume between baseline and follow-up to identify patients who had tissue at risk of infarction at
baseline. Treatment with recombinant tissue plasminogen activator or enrollment in trials of neuroprotective agents versus placebo was allowed. The following clinical characteristics were recorded: age, National Institutes of Health Stroke Scale (NIHSS) score, time from symptom onset to MR, and Trial of Org 10172 in Acute Stroke Treatment (TOAST) subtype.9 The study was approved by the Stanford Institutional Review Board.

Imaging and Postprocessing

MRI
MRI was performed with echo planar imaging on a 1.5-T General Electric Signa magnet. Multislice whole-brain DWI was performed with the following parameters: slices, 16; repetition time, 8100 ms; echo time, 110 ms; slice thickness, 5 mm; gap, 2.5 mm; matrix, 128×128; and field of view, 24 cm. The b values were 0 and 829 s/mm². DWI scans were acquired with diffusion encoding along the x, y, or z direction. The x-, y-, and z-direction DWI scans were averaged to minimize hyperintensities resulting from anisotropic water diffusion.

PWI was performed with dynamic susceptibility contrast-enhanced MRI. Gradient echo, single-shot echo planar imaging was used during injection of gadolinium (0.2 mmol/kg). PWI acquisition values were as follows: repetition time, 2000 ms; and echo time, 60 ms, obtained over 12 slices (40 time points each). Other parameters were the same as for DWI. The 12 PWI slices were taken at the same level as the 12 central slices on the DWI scans.

Postprocessing of Perfusion Images
The bolus-tracking raw images were realigned with automated image registration.10 PWI maps were calculated with the truncated singular value decomposition method described by Overgaard et al11,12 using previously described software.13 The tissue concentration over time curve was deconvolved with AIF using the truncated singular value decomposition method to obtain the residue function. The residue function is the amount of tracer that remains in the voxel of interest over time after an idealized, instantaneous bolus of contrast. No analytical fit of AIF was performed. AIF was measured at 4 locations: near the contralateral and ipsilateral middle cerebral arteries in the M1 and M2 segments (AIFCMCA and AIFIMCA), in middle cerebral artery (MCA) branches adjacent to the largest diffusion abnormality (AIFIDWI), and at the same level on the opposite hemisphere (AIFTIOMA). The pixels chosen to determine AIF had to show an early rise of intensity and a large increase in intensity on the tissue concentration–time curve compared with normal brain parenchyma. Although no formal quantitative criterion was used to determine AIF, quantitative information regarding the onset of the intensity increase and the area under the curve (AUC) was continuously available when AIF was selected. The AUC of the AIF was measured by integrating the relaxivity-over-time curve (Figure 1) This AUC measurement is biased because no method was used to eliminate recirculation. An unbiased AUC is required to determine CBF, cerebral blood volume, and mean transit time accurately. However, an accurate determination of the AUC is not required for determining the Tmax parameter used in our study. Tmax is a hemodynamic parameter that estimates the delay of the peak of the tissue residue function obtained by deconvolution.14 Tmax allows rapid visual identification of areas with varying degrees of hypoperfusion.

Lesion volume measurements on DWI and PWI images were performed by a semiautomated method using a threshold function. The threshold for defining a pathological DWI hyperintensity was chosen as 3 SD above the mean normal DWI signal intensity determined from a reference region containing both white and gray matter in the contralateral hemisphere. PWI abnormalities were defined as the areas of hypoperfusion with a Tmax delay of ≥2 seconds. This threshold was chosen because visual analysis of Tmax >1 second showed this threshold to be overly sensitive. Tmax lesions of >6 and 8 seconds were recently shown to have a high likelihood of subsequent infarction.15 A PWI-DWI mismatch was defined as a baseline hypoperfusion lesion volume that was ≥120% the volume of the baseline diffusion lesion volume.

Interobserver Reliability
Two independent observers (V.T., D.S.) independently measured AIF to assess interobserver reliability in a subset of 10 randomly chosen patients. The volumes obtained with the AIF at the different locations by each observer were compared, and the intraclass correlation coefficients were measured for each location.

Statistical Analysis
The AUCs of AIFs obtained at different locations were compared by use of Friedman’s test. Pairwise comparisons were then performed by use of Wilcoxon’s paired rank-sum test to determine significant differences among AIFs at different locations. Hypoperfusion lesion volumes with AIFs obtained from different locations were compared with the follow-up DWI lesion volume through paired t tests. Regression analysis was used to identify the hypoperfusion lesion volume that was most closely associated with the DWI lesion volume at follow-up. All statistical tests were 2 tailed, and a value of P=0.05 was considered significant. All statistical tests were performed with SPSS 10.0.

Results
Patients
We identified 30 patients who underwent DWI and PWI within 8 hours of symptom onset between August 1, 1996,
Clinical and Volumetric Lesion Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline NIHSS</th>
<th>TOAST Classification Subtype</th>
<th>DWI Volume Baseline</th>
<th>DWI Volume at 4 – 6 Days</th>
<th>PWI Volume From AIF CMCA</th>
<th>PWI Volume From AIF IDWI</th>
<th>PWI Volume From AIF IMCA</th>
<th>PWI Volume From AIF CDWI</th>
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<td>114.4</td>
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<td>54.7</td>
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</table>

*Volumes are in milliliters.

*This patient had atrial fibrillation and a high-grade carotid stenosis ipsilateral to the ischemic lesion.

and August 1, 2000. In 4 patients, poor image quality resulting from motion artifact or inadequate bolus delivery prevented analysis of the perfusion images. Three patients did not have repeated imaging within 4 to 7 days after symptom onset. Ten patients did not have lesion growth between baseline and follow-up. This left 13 patients for analysis. The median baseline DWI lesion was 28 cm³ (25th percentile, 22.4; 75th percentile, 84.4). One patient did not have a baseline DWI lesion. Follow-up images were obtained a median of 5.15 days (range, 4 to 6.4 days) after symptom onset. Lesion volumes increased a median of 227% (25th percentile, 147%; 75th percentile, 279%) between baseline and follow-up.

Nine patients were enrolled in trials of neuroprotective agents versus placebo (cervene, n = 5; lubeluzole, n = 4). One patient received tissue plasminogen activator and was enrolled in a neuroprotective agent trial (lubeluzole). One patient was treated with tissue plasminogen activator according to the National Institute of Neurological Disorders and Stroke criteria. Patients treated with thrombolytics were imaged with MRI as soon after treatment as possible.

Interobserver Reliability

The intraclass correlation coefficients for measurement of the volumes of hypoperfusion using AIFs from different locations were 0.89 with AIFCDWI and 0.87 with AIFIDWI. The intraclass correlation coefficient was 0.93 with AIFCMCA and 0.88 with AIFIMCA.

AIF Characteristics

The AUCs of AIFs obtained at different locations were significantly different (P < 0.0001). The AUC of AIFCMCA (median, 937; interquartile range [IQR], 672 to 1036) was significantly larger than the AUC of AIFIDWI (median, 413; IQR, 278 to 529; P = 0.001) and AIFCDWI (median, 588; IQR, 377 to 723; P = 0.003). The AUC of AIFCMCA tended to be larger than the AUC from AIFIMCA (median, 764; IQR, 598 to 930; P = 0.08). The AUC of AIFIMCA was significantly larger than the AUC of AIFIDWI (P = 0.001) and tended to be larger than that of AIFCDWI (P = 0.055). The last AUC was larger than the AUC of AIFCDWI (P = 0.039).

Volume Characteristics

Large variations in PWI lesion size were found with different AIF locations (the Table). The largest PWI lesions were found when AIF was measured at the contralateral MCA. These PWI lesions were significantly larger than the PWI lesions obtained with AIFIMCA (mean difference, 60 mL; P = 0.0022), AIFCDWI (mean difference, 37.3 cm³; P = 0.0054), and AIFIDWI (mean difference, 77.8; P = 0.0001). The volumes obtained with AIFCMCA Spatially enclosed the volumes identified with other AIFs. The volumes obtained with AIFIMCA, AIFCDWI, and AIFIDWI significantly underestimated the final lesion volume. There was no significant difference between the volumes obtained with AIFCMCA at baseline and the final lesion volume (mean difference, 12.16 cm³; 95% confidence interval, −40.8 to 16; P = 0.37). Regression analysis showed that this PWI lesion was associated with final lesion volume (R = 0.6, P = 0.002; Figure 2). These differences remained...
significant after exclusion of the 3 patients with ipsilateral high-grade carotid artery stenosis.

The PWI/DWI mismatch frequency was 100% (13 of 13) with AIF CMCA, 77% (10 of 13) with AIF CDWI, 38.5% (5 of 13) with AIF IMCA, and 23% (3 of 13) with AIF IDWI. Figure 3 shows baseline PWI maps of a patient scanned 6.8 hours after symptom onset with an NIHSS of 13.

Discussion

Our study shows that AIF is an important determinant of the size of hypoperfusion lesion as measured with Tmax. PWI lesion volumes determined with AIF from the contralateral MCA were associated with follow-up lesion volumes, whereas volumes obtained with other AIFs overestimated or underestimated follow-up DWI lesion volumes. Our study suggests that the optimal location to determine AIF is in the M1 or M2 segment of the MCA in the hemisphere opposite the hypoperfusion lesion.

To include patients who had tissue at risk of infarction at baseline, we studied only patients who exhibited lesion growth between baseline and follow-up. Several patients had a mismatch (PWI>DWI) when AIF was measured in 1 location and did not exhibit a mismatch with another AIF. To determine the optimal location for measurement of the AIF, we did not include patients on the basis of the presence or absence of a mismatch because this would create a bias favoring 1 location over another.

The AIF with the largest AUC was AIF CMCA, followed by AIF ICMA, AIF CDWI, and AIF IDWI. The differences between the ipsilateral and contralateral AUCs of the AIF are related to

![Figure 2](image2.png)

**Figure 2.** Correlations between baseline PWI lesion volume obtained with different AIFs and DWI lesion volume at days 4 to 7. Continuous line represents fitted curve obtained by regression analysis between these 2 variables.

![Figure 3](image3.png)

**Figure 3.** Baseline PWI maps of patient 10 scanned 6.8 hours after symptom onset with an NIHSS of 13. PWI determined from AIFCDWI (A), AIFCMCA (B), AIFCDWI (C), and AIFCMCA (D). E, DWI lesion at follow-up. PWI maps shown are an overlay of pixels with Tmax $\geq$ 2 seconds on the baseline T2*-gradient echo slice. The majority of pixels within this lesion have Tmax $\geq$ 4 seconds.
the difficulty of choosing pixels that are not affected by hypoperfusion on the ipsilateral side of the ischemic lesion without knowing a priori the extent of hypoperfusion. The differences between AIF from the MCA stem and from smaller MCA branches are probably due to the caliber variation between these vessels and larger partial volume effects within smaller vessels.

A few studies have examined the relationship between AIF location and the size and severity of perfusion abnormalities. Ostergaard et al\textsuperscript{12} found similar shapes of AIF when measured at different brain locations, but no volumetric data were provided. Lythgoe et al\textsuperscript{18} compared the CBF values in gray matter generated by the use of AIFs from either the contralateral or the ipsilateral MCA in patients with carotid stenosis or occlusion. CBF estimations were different between the ipsilateral and contralateral arteries, and those authors suggested using the contralateral MCA in patients with high-grade carotid stenosis. A recent study, however, found no difference in CBF values in patients with carotid occlusion when AIF was obtained ipsilateral or contralateral to the stenosis or occlusion in 6 of 7 patients. In 1 patient, a significant difference was found.\textsuperscript{19} Another study in normal subjects found significant differences in AIF shape between the MCA and the internal carotid and vertebral arteries.\textsuperscript{20}

This study has several limitations. The sample size was small; therefore, these findings need to be reproduced in a larger sample of patients. Several patients were treated with intravenous tissue plasminogen activator or with putative neuroprotective agents. In these patients, the amount of lesion growth between baseline and follow-up might have been different without treatment. Vasogenic edema might also have contributed to the volume increases between the 2 time points. We included 3 patients with high-grade carotid artery stenosis ipsilateral to the ischemic lesion. The volume of hypoperfusion might be exaggerated in these patients.\textsuperscript{21} However, exclusion of these patients in our sample did not significantly change our findings.

PWI has not been validated against the gold standard of PET in patients with acute ischemic stroke. Several other shortcomings of this technique have been highlighted recently. These include bias introduced by bolus delay and dispersion, assumptions about tissue hematocrit, and biased measurement of AIF by partial volume effects.\textsuperscript{3,6} Tmax is less commonly used as a perfusion parameter.\textsuperscript{13,14} Future studies should examine the relationship between Tmax and other hemodynamic parameters and determine whether AIF location also influences the volumes of these PWI lesions.

In conclusion, we found that AIF is a major determinant of the size of hypoperfusion lesions obtained with PWI. PWI lesion volumes determined with AIF from the contralateral MCA are associated with the follow-up lesion volume and might be used in conjunction with DWI to identify tissue at risk of infarction.

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References
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