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

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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
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. 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. PWI maps were calculated with the truncated singular value decomposition method described by Ostergaard et al using previously described software. 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 AIFmca), in middle cerebral artery (MCA) branches adjacent to the largest diffusion abnormality (AIFdmca), and at the same level on the opposite hemisphere (AIFcmca). 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 1A) 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. 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. 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,
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 volume was 28 cm$^3$ (25th percentile,
5.6; 75th percentile, 147%; interquartile range [IQR], 278 to 529;)
between baseline

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<th>PWI Volume From AIF$^*_{CDWI}$</th>
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*Volume of final lesion calculated from PWI. AIF$^*_{IMCA}$, AIF$^*_{CDWI}$, and AIF$^*_{IDWI}$ significantly underestimated the final lesion volume. The volumes obtained with AIF$^*_{CMCA}$ spatially enclosed the volumes identified with other AIFs. The volumes obtained with AIF$^*_{IMCA}$, AIF$^*_{CDWI}$, and AIF$^*_{IDWI}$ significantly underestimated the final lesion volume. There was no significant difference between the volumes obtained with AIF$^*_{CMCA}$ at baseline and the final lesion volume (mean difference, 12.16 cm$^3$; 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

AIF Characteristics

The AUCs of AIFs obtained at different locations were significantly different ($P<0.0001$). The AUC of AIF$^*_{CMCA}$ (median, 937; interquartile range [IQR], 672 to 1036) was significantly larger than the AUC of AIF$^*_{IDWI}$ (median, 413; IQR, 278 to 529; $P=0.001$) and AIF$^*_{CDWI}$ (median, 588; IQR, 377 to 723; $P=0.003$). The AUC of AIF$^*_{CMCA}$ tended to be larger than the AUC from AIF$^*_{IMCA}$ (median, 764; IQR, 598 to 930; $P=0.08$). The AUC of AIF$^*_{IMCA}$ was significantly larger than the AUC of AIF$^*_{IDWI}$ ($P=0.001$) and tended to be larger than that of AIF$^*_{CDWI}$ ($P=0.055$). The last AUC was larger than the AUC of AIF$^*_{IDWI}$ ($P=0.039$).
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...
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. found similar shapes of AIF when measured at different brain locations, but no volumetric data were provided. Lythgoe et al. 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. Another study in normal subjects found significant differences in AIF shape between the MCA and the internal carotid and vertebral arteries.

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. 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. Tmax is less commonly used as a perfusion parameter. 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**
