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 imaging (DWI) and perfusion-weighted imaging (PWI) 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.

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
Arterial Input Function and Hypoperfusion Volumes

**Results**

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. 13 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. 14 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.

**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>TOAST Classification</th>
<th>Baseline NIHSS</th>
<th>Baseline DWI Volume</th>
<th>PNI Volume From AIFIMCA</th>
<th>PNI Volume From AIFCDWI</th>
<th>PNI Volume From AIFIDWI</th>
<th>PNI Volume From AIFCMCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cardioembolic</td>
<td>23.1</td>
<td>30.5</td>
<td>61.4</td>
<td>38.5</td>
<td>68.9</td>
<td>30.4</td>
</tr>
<tr>
<td>2</td>
<td>Cardioembolic</td>
<td>28.3</td>
<td>65.2</td>
<td>50.9</td>
<td>45.6</td>
<td>24.3</td>
<td>18.2</td>
</tr>
<tr>
<td>3</td>
<td>Cardioembolic</td>
<td>153.3</td>
<td>202.8</td>
<td>217.2</td>
<td>215.9</td>
<td>141.5</td>
<td>133.2</td>
</tr>
<tr>
<td>4</td>
<td>Large vessel</td>
<td>30.8</td>
<td>68</td>
<td>64.1</td>
<td>9.0</td>
<td>210</td>
<td>5.0</td>
</tr>
<tr>
<td>5</td>
<td>Cardioembolic</td>
<td>24.7</td>
<td>55.6</td>
<td>140.0</td>
<td>12.4</td>
<td>12.7</td>
<td>6.9</td>
</tr>
<tr>
<td>6</td>
<td>Cryptogenic</td>
<td>0.0</td>
<td>109.1</td>
<td>155.0</td>
<td>78.1</td>
<td>149.7</td>
<td>83.0</td>
</tr>
<tr>
<td>7</td>
<td>Cryptogenic*</td>
<td>109.2</td>
<td>208.1</td>
<td>267.3</td>
<td>196.2</td>
<td>69.2</td>
<td>56.2</td>
</tr>
<tr>
<td>8</td>
<td>Cryptogenic</td>
<td>35.2</td>
<td>112.8</td>
<td>85.6</td>
<td>88.1</td>
<td>33.0</td>
<td>20.4</td>
</tr>
<tr>
<td>9</td>
<td>Cardioembolic</td>
<td>9.1</td>
<td>86.3</td>
<td>38.2</td>
<td>58.5</td>
<td>18.2</td>
<td>3.1</td>
</tr>
<tr>
<td>10</td>
<td>Large vessel</td>
<td>8.2</td>
<td>70.4</td>
<td>117.6</td>
<td>90.0</td>
<td>44.0</td>
<td>35.1</td>
</tr>
<tr>
<td>11</td>
<td>Cardioembolic</td>
<td>100.8</td>
<td>239.3</td>
<td>156.7</td>
<td>113.4</td>
<td>65.1</td>
<td>77.1</td>
</tr>
<tr>
<td>12</td>
<td>Cardioembolic</td>
<td>27.7</td>
<td>29.8</td>
<td>30.4</td>
<td>2.6</td>
<td>6.0</td>
<td>2.2</td>
</tr>
<tr>
<td>13</td>
<td>Cryptogenic</td>
<td>22.1</td>
<td>51.4</td>
<td>102.8</td>
<td>54.4</td>
<td>57.3</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Mean, 95% CI 13 patients

|                        | (15.9–72.1) | (59.8–144.7) | (71.2–157.6) | (37.0–117.2) | (27.0–82.4) | (12.4–60.9) |

Volumes are in milliliters.

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

Volumes were calculated from baseline DWI, baseline NIHSS, baseline TOAST Classification, baseline DWI volume, PNI volume from AIFIMCA, PNI volume from AIFCDWI, PNI volume from AIFIDWI, PNI volume from AIFCMCA, PNI volume from AIFIDWI, and PNI volume from AIFCDWI. Values are presented as mean, 95% confidence interval.

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 time between baseline and MRI was a median of 5.15 hours (25th percentile, 4.03; 75th percentile, 6.40). The median baseline DWI volume was 28 cm$^3$ (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 5.1 days (range, 4 to 6.4 days) after symptom onset. Lesion volumes increased a median of 227% (25th percentile, 15.9–72.1). The etiologic classification of strokes was cardioembolic in 7 patients (54%), large-vessel disease in 2 (15%), and cryptogenic in 4 patients (31%). One of the cryptogenic patients had an ipsilateral high-grade carotid stenosis and atrial fibrillation. A high-grade carotid stenosis ipsilateral to the cerebral ischemia was therefore present in 3 patients in total.

The time between baseline and MRI was a median of 5:15 hours (25th percentile, 4:03; 75th percentile, 6:40). The median baseline DWI volume was 28 cm$^3$ (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 5.1 days (range, 4 to 6.4 days) after symptom onset. Lesion volumes increased a median of 227% (25th percentile, 15.9–72.1; 75th 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 AIFIDWI ($P=0.039$).

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 AIFCMCA (mean difference, 60 mL; $P=0.0022$), AIFCDWI (mean difference, 37.3 cm$^3$; $P=0.0054$), 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 AIFCMCA, 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 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
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_CMA, 77% (10 of 13) with AIF_CDWI, 38.5% (5 of 13) with AIF_MCMA, 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_CMA, followed by AIF_CMCA, AIF_CDWI, and AIF_IDWI. The differences between the ipsilateral and contralateral AUCs of the AIF are related to

**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.** Baseline PWI maps of patient 10 scanned 6.8 hours after symptom onset with an NIHSS of 13. PWI determined from AIF_IDWI (A), AIF_CMCA (B), AIF_CDWI (C), and AIF_CMCA (D). E, DWI lesion at follow-up. PWI maps shown are an overlay of pixels with Tmax >2 seconds on the baseline T2*-gradient echo slice. The majority of pixels within this lesion have Tmax >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. 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.

**Acknowledgments**

Dr. Thijs is supported by the Fonds voor Wetenschappelijk Onderzoek Vlaanderen. This study was supported in part by NIH grants NS-34088–03, R01 NS35959, and R01 NS34866–06.

**References**


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

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

Stroke. 2004;35:94-98; originally published online December 11, 2003;
doi: 10.1161/01.STR.0000106136.15163.73

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/35/1/94

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/