Reliable Perfusion Maps in Stroke MRI Using Arterial Input Functions Derived From Distal Middle Cerebral Artery Branches

Martin Ebinger, MD; Peter Brunecker, MSc; Gerhard J. Jungehülslng, MD; Uwe Malzahn, NatScD; Claudia Kunze; Matthias Endres, MD; Jochen B. Fiebach, MD

Background and Purpose—Perfusion imaging is widely used in stroke, but there are uncertainties with regard to the choice of arterial input function (AIF). Two important aspects of AIFs are signal-to-noise ratio and bolus-related signal drop, ideally close to 63%. We hypothesized that distal branches of the middle cerebral artery (MCA) provide higher quality of AIF compared with proximal branches.

Methods—Over a period of 3 months, consecutive patients with suspected stroke were examined in a 3-T MRI scanner within 24 hours of symptom onset. AIFs were selected manually in M1, M2, and M3 branches of the MCA contralateral to the suspected ischemia. Signal-to-noise ratio and bolus-related signal drop were analyzed. Perfusion maps were created for every patient and mean values at the insular level as well as relative ranges were compared.

Results—Mean age of 132 included patients (53 females) was 67.3 years (SD, 14.9) and median National Institutes of Health Stroke Scale was 3 (interquartile range [IQR] 0 to 6). For further analyses, 4 patients were excluded due to discontinuation of scanning or insufficient bolus arrival (signal drop <15%). Median signal-to-noise ratio was highest in M3 branches (36.41; IQR, 29.29 to 43.58). Median signal-to-noise ratio in M2 branches was intermediate (27.54; IQR, 20.78 to 34.00) and median signal-to-noise ratio in M1 was low (12.40; IQR, 9.11 to 17.15). Using AIFs derived from M1 and M2 branches of the MCA median signal drop was 77% (IQR, 72% to 82%) and 78% (IQR, 73% to 83%), respectively. Signal drop was significantly reduced when AIF was selected in M3 branches with a median of 72% (IQR, 63% to 77%; P<0.01). Highest variability of 3456 perfusion maps was found in those derived from M1.

Conclusion—The level of AIF selection in the MCA has a major impact on reliability and even quantitative parameters of perfusion maps. For better comparison of perfusion maps, the AIF should be defined by selection of distal branches of the MCA contralateral to the suspected ischemia. In future trials involving perfusion imaging, the MCA segment used for the AIF should be specified. (Stroke. 2010;41:95-101.)

Key Words: arterial input function ■ MRI ■ perfusion ■ stroke

Salvage of hypoperfused but not yet irreversibly damaged brain tissue is the aim of thrombolytic treatment. A mismatch between a larger perfusion deficit and a smaller lesion on diffusion-weighted MRI is the most common clinical approach to identify this tissue at risk.1 However, there is an ongoing discussion concerning what parameters provide the best definition of a perfusion deficit.2 We argue that before this discussion, more attention should be focused on the preconditions of perfusion imaging. Perfusion maps as calculated from dynamic susceptibility-enhanced contrast MRI depend on the arterial input function (AIF). The AIF reflects the arterial concentration of a contrast agent in the feeding vessel distributed in time. Ideally, the administered contrast agent arrives in the vasculature of the brain at a single moment as a bolus. In fact, however, the arrival and disappearing of an intravenously injected bolus takes time. To correct for this, and for modification of the bolus by dispersion during transport, deconvolution of the bolus shape is applied, resulting in a tissue concentration curve as if derived from an infinitely short bolus. Volumes of perfusion deficits determined with AIF from the contralateral middle cerebral artery (MCA) were associated with follow-up lesion volumes.3 This suggested that the contralateral MCA might be the most appropriate vascular territory for selection of AIFs. However, the optimal location within the vascular bed of the contralateral MCA is unknown. Influences on the AIF through distortion by saturation issues, partial volume effects, and spatial distortion due to local frequency shifts are

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frequently discussed. Although these are important topics, some further preconditions for reliable perfusion imaging have been eclipsed. One of these essential preconditions is a high intrinsic signal-to-noise ratio. Another one is the bolus-related signal drop. The optimal yield of processable signal can be obtained when the MR intensity curve falls by 63% of the prebolus signal intensity. The prebolus signal-to-noise ratio (SNR$_{pre}$) is the ratio of the signal intensity over its standard deviation before bolus arrival. A high SNR$_{pre}$ is a requirement for precision of dynamic perfusion imaging and is believed to be technically determined by sequence- and scanner-inherent conditions. However, other factors vary from scan to scan. For instance, deconvolution of tissue with arterial input depends on the concentration curve of a particular contrast agent. Due to individual cardiac output or differences in total blood volume, the signal drop during passage of the contrast bolus may vary as well.

Based on our clinical experience, we had the impression that SNR$_{pre}$ was higher in distal versus proximal branches. In a prospective cohort of consecutive patients with stroke, we assessed the hypothesis that distal branches of the MCA provide higher quality of AIF in terms of SNR$_{pre}$ and bolus-related signal drop compared with proximal branches. We further investigated the impact the MCA segment chosen for AIF had on quantitative parameters (mean values) and reliability (relative ranges) of perfusion maps.

### Subjects, Materials, and Methods

#### Patients

Over a period of 3 months, consecutive patients ≥18 years of age with suspected stroke were examined within 24 hours after symptom onset. Exclusion criteria were inability to undergo MRI and/or history of renal failure. Written consent was provided by the patient or legal representative according to the institutional protocol. The study protocol was approved by the local ethics committee. This is a substudy of the clinical trial NCT00715533 (ClinicalTrials.gov).

#### Perfusion Imaging

MR studies were performed on a 3-T MRI system equipped with echoplanar imaging capabilities (Tim Trio; Siemens AG). Slice location was in the AC–PC orientation. For perfusion measurements, 5 mL Gadovist (1 mol/L Gadobutrol; Bayer Schering Pharma AG) followed by 20 mL saline was injected at a rate of 5 mL/s using a power injector (Spectris; Medrad Inc). In patients weighing ≥100 kg, 6 mL was injected and in patients weighing ≥50 kg, 4 mL was injected. Bolus track MRI was performed on patients with stroke using an echoplanar imaging gradient echo sequence (TE=29 ms; TR=1390 ms; matrix size=128×128; field of view=230 mm; slice thickness=5 mm). Data acquisition started 10 seconds before contrast agent injection and continued for 118 seconds.

#### Preprocessing

To check for cerebral bolus arrival, average signal drop within a whole slice at the insular level was calculated. Signal drop <15% was deemed insufficient for further analyses. The concentration curve, c(t), was calculated from measured signal changes, S(t), by

\[
c(t) = -kT_E^e \log \left( S(t)/S(t=0) \right)
\]

where $T_E$ is the echo time and $k$ is a factor depending on tracer dosage, partial blood volume, hematocrit, MR sequence, and the scanning device. To obtain normalized tracer concentration, the calibration factor $k$ in Eq. 1 was set to $T_E$.

#### AIF Selection

AIFs were selected manually by an experienced neuroradiologist (J.B.F.) using previously developed in-house software. For each MCA segment (M1, M2, and M3) contralateral to the suspected ischemia, 3 voxels were chosen in every patient (Figure 1). Levels for voxel selection within the vascular territory of the MCA were defined as base of the skull, insula, and top of the ventricle for M1, M2, and M3, respectively. AIFs from these voxels were selected using subjective criteria of an early, steep rise in c(t), a smooth shape of the curve, and a quick return to baseline. The neuroradiologist was instructed to select those AIFs that he would have used in clinical routine. Additionally, in all 3 slices containing M1, M2, and M3 segments of the MCA, voxels were automatically selected based on a threshold criterion (initial signal intensity ≥200; GNU Octave, www.octave.org). This was done to generate a tissue-like reference for the 3 different arterial selections on the same spatial level.

#### Postprocessing

For each AIF, we studied its quality by determining SNR$_{pre}$ and bolus-related signal drop in each patient. Results from each segment were finally averaged, for example, SNR$_{pre}$ of the 2 AIFs derived from M1 were averaged and subsequently treated as the SNR$_{pre}$ of M1. Furthermore, to demonstrate the effects on the resulting perfusion maps, we determined the mean value of 3 perfusion maps, namely mean transit time (MTT), cerebral blood volume (CBV), and cerebral blood flow (CBF), at the insular level of perfusion maps derived from AIFs using each of the 3 locations chosen within M1, M2, and M3 branches in each patient (3×3 uniform spatial raw data filter, truncated singular value decomposition with a 10% cutoff). To compare the effects of AIF determination in different MCA segments, we calculated the mean values of the parameters MTT, CBV, and CBF, respectively, at the insular level for each single AIF separately. The difference of the maximal and the minimal value (the range) in each MCA level (M1, M2, and M3) was consecutively divided by the mean value in the MCA level, respectively, to provide a relative range as a measure of uncertainty.

#### Statistical Analyses

Prebolus signal intensity, its SD, SNR$_{pre}$, and bolus-related signal drop were analyzed using Wilcoxon test. Medians of these parameters were compared among M1, M2, and M3 branches and between whole slices at the corresponding levels. Subsequently, each parameter of each branch was compared with the corresponding value of the corresponding whole slice. The assumption of normal distribution for the mean or relative range data of the perfusion maps was assessed by the Shapiro-Wilk test. The Friedman test was used to determine whether significant differences between means/relative ranges among the MCA segments (M1, M2, M3) existed. To keep the number of pairwise comparisons to a minimum, they were only performed in case of data with significant differences. We applied the nonparametric Wilcoxon test for paired samples. We checked whether the resulting probability values represented significant results by 2 procedures for multiple testing: Bonferroni-Holm (“step up”) and Hochberg (“step down”). We considered 3 families of tests for which errors were controlled jointly: MTT, CBV, and CBF. The term “significant” was used for $P<0.05$.

#### Results

We included 132 patients (53 females) in this study. Mean age of patients was 67.3 years (SD, 14.9) and median National Institutes of Health Stroke Scale was 3 (interquartile range [IQR], 0 to 6). Perfusion imaging was well tolerated and no adverse events have been observed. One patient was not included in further analysis because he had refused continuation of the scanning during perfusion measurement.
for an unknown reason. Of the remaining 131 patients, 3 patients were excluded because whole slice analysis at the insular level revealed a signal drop <15%.

### Prebolus Signal-to-Noise Ratio

Medians of prebolus signal intensity, its SD, and SNR\(_{\text{pre}}\) for M1, M2, M3 and for whole slices at the corresponding levels are given in Table 1. Prebolus signal intensity increased from proximal to distal branches, whereas SD decreased from proximal to distal branches. This resulted in the highest SNR\(_{\text{pre}}\) in M3 branches of the MCA. The SNR\(_{\text{pre}}\) in M2 branches was intermediate and the SNR\(_{\text{pre}}\) in M1 was low. Although 42 patients had a SNR\(_{\text{pre}}\) <10 in M1, all patients had SNR\(_{\text{pre}}\) >10 in M2 and M3 branches (Figure 2). Compared with the corresponding whole slices, SDs were higher, whereas signal intensities were lower in MCA branches. This resulted in lower SNR\(_{\text{pre}}\) in all MCA branches compared with the corresponding whole slice (Table 1).

![Figure 1. Exemplary selection of voxels for AIF determination at M1 (A), M2 (B), and M3 (C) in one patient (upper images) with the resulting AIFs (beneath). Note the increased noise in AIFs derived from M1 compared with M2 and M3.](image)

<table>
<thead>
<tr>
<th>MCA Branch or Slice Level</th>
<th>Prebolus Signal Intensity Median (IQR)</th>
<th>SD of Prebolus Signal Intensity Median (IQR)</th>
<th>SNR Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>456.19 (361.46–549.04)</td>
<td>38.82 (28.29–49.09)</td>
<td>12.40 (9.11–17.15)</td>
</tr>
<tr>
<td>Slice at M1</td>
<td>571.15 (539.95–597.12)</td>
<td>19.30 (17.80–21.43)</td>
<td>35.09 (32.16–38.13)</td>
</tr>
<tr>
<td>M2</td>
<td>646.74 (606.93–698.51)</td>
<td>25.42 (20.77–32.07)</td>
<td>27.54 (20.78–34.00)</td>
</tr>
<tr>
<td>Slice at M2</td>
<td>637.01 (606.47–663.22)</td>
<td>16.30 (14.62–18.67)</td>
<td>43.36 (39.18–47.15)</td>
</tr>
<tr>
<td>M3</td>
<td>676.71 (625.00–723.26)</td>
<td>19.90 (16.40–25.70)</td>
<td>36.41 (29.29–43.58)</td>
</tr>
<tr>
<td>Slice at M3</td>
<td>684.49 (656.97–720.33)</td>
<td>15.27 (13.74–17.86)</td>
<td>49.15 (44.67–53.64)</td>
</tr>
</tbody>
</table>

Comparison M1 versus slice each comparison \(P < 0.05\)

Group comparison M1 < M2 < M3, S1 < S2 < S3 each comparison \(P < 0.05\)

Group comparison M1 < M2 < M3, S1 < S2 < S3 each comparison \(P < 0.05\)

Group comparison M1 < M2 < M3, S1 < S2 < S3 each comparison \(P < 0.05\)

*Among the MCA segments, highest signal intensity and lowest noise was found in M3 branches. Despite overlap with regard to IQRs of some parameters, Wilcoxon nonparametric test revealed significant differences for comparisons of prebolus signal intensity, noise, and SNR between MCA segments and whole slices as well as for all comparisons among MCA segments and for all comparisons among whole slices.*
Signal Drop
A clustering of signal drop close to 80% was observed when using AIFs derived from M1 and M2 branches of the MCA (median, 77%; IQR, 72% to 82%; median, 79%; IQR, 74% to 84%, respectively). Signal drop was significantly reduced when AIF was selected in M3 branches compared with M1 and M2 ($P<0.001$) with a median of 72% (IQR, 63% to 78%).

Effects on Perfusion Maps
We determined the mean value and the relative range of 3456 perfusion maps (3 perfusion parameters $\times$ 3 voxels $\times$ 3 MCA branches $\times$ 128 patients). The Shapiro-Wilk test revealed that the assumption of normal distribution is not justified for the mean or the relative range data of the perfusion maps. Using the Friedman test, we detected significant differences between the means as well as between the relative ranges among the MCA segments (M1, M2, M3) for MTT maps. The same is true for CBV maps. For CBF maps, significant differences were shown for the means, but not for the relative ranges. Therefore, we performed pairwise comparisons between means and relative ranges for MTT and CBV maps and pairwise comparisons between means for CBF maps to test the hypothesis of equality. Both “step up” and “step down” procedures corroborated that the probability values represented significant results. Table 2 shows that the mean MTT value decreased if AIF was taken from more distal branches, whereas the mean CBF value increased and the mean CBV value was slightly lower in maps derived from M2 branches compared with M1 and M3. For all perfusion parameters tested, the relative range was highest in maps derived from M1. The relative range of perfusion maps derived from M2 and M3 branches did not differ significantly (Table 2).

Discussion
There were 2 major findings in this study. First, high SNR$_{pre}$ and superior bolus-related signal drop in AIFs derived from distal branches of the MCA resulted in more reliable perfusion maps. Second, the absolute values of perfusion maps differed depending on the MCA branch chosen for AIF selection.

We refined the findings from Thijs and colleagues who concluded that the AIF should be derived from the contralateral MCA. Thijs et al measured the AIF near the contralateral and ipsilateral MCAs in the M1 and M2 segments, in MCA branches adjacent to the largest diffusion abnormality, and at the same level on the opposite hemisphere. They did not specifically consider M3 branches. Furthermore, our study was a practical application of the theoretical findings by Smith and colleagues. They varied experimental contrast concentration level and echo time to find the optimal yield of processable signal. This was achieved when the MR intensity curve dropped by 63% of the prebolus signal intensity. Although this is the best evidence available at this point in time, it is based on phantom measurements and there is no scientific proof that the ideal of a 63% drop can be translated to in vivo measurements. However, until proven otherwise, it is intuitively plausible that the theoretical and experimental results by Smith et al apply to patients also.

It was previously shown that SNR$_{pre} < 10$ leads to systematically erroneous maps. Although many patients had such an unacceptably low SNR$_{pre}$ ($n=42$) when the AIF was derived from the level of M1, AIF derived from levels of M2 and M3 branches resulted in SNR$_{pre} > 10$ in all patients. The bulk of the noise in MRI is explained by intrinsic scanner noise independent of the location selected for measurement. The good SNR$_{pre}$ in M3 branches is due to both higher signal and reduced noise (Table 1). Pulsation artifacts in more proximal branches may be one of the reasons for worse
SNR<sub>pre</sub> in proximal branches. The anatomic location close to the skull base is prone to artifacts, which is a further disadvantage of M1. In contrast, distal arteries have advantages in terms of reduced delay and dispersion. Compared with large arteries, they further have the advantage that even voxels including the vessel still yield adequate AIF measurements. Despite the influence of the corresponding slice level from which the AIF was derived, we demonstrated that there were significant differences between results of whole slice analyses and MCA branch analyses. Noise of the whole slice at the level of M1 was half of that measured at the artery, but this difference between whole slice analyses and corresponding artery decreased with higher levels (Table 1). This leads to the assumption that there are unknown factors specific to the arteries, which influenced the SNR<sub>pre</sub> to an extent exceeding that attributable to whole slice phenomena.

A limitation of our study is that we did not account for the role of partial volume effects. We did not control for orientation or size of the vessel used. It was not specified whether to select an area adjacent or within an identifiable artery. Rather, the neuroradiologist was encouraged to select those voxels within the predefined levels that provided AIFs he would have used in clinical routine. We cannot exclude a systematic influence on the absolute values of perfusion maps due to vessel size and partial volume effects. Partial volume effects may introduce variability of the AIF. However, assuming a reduced contribution of tissue signal when placing AIFs within larger arteries, this cannot explain the improved reliability of perfusion maps derived from smaller distal branches. A further limitation of our study was that we only used 2 criteria to determine the quality of AIFs. Nevertheless, this was sufficient to show statistically significant differences between the perfusion maps and therefore corroborated the importance of these factors. We did not study interrater variability and we did not use different types of scanners. All images were acquired from a single 3-T

<table>
<thead>
<tr>
<th>Perfusion map</th>
<th>MCA segment used for AIF</th>
<th>Parameter Value of map (insular level)</th>
<th>P-value (Wilcoxon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTT</td>
<td>M1</td>
<td>Mean 6.30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative Range 0.78</td>
<td>0.0015</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>Mean 5.68</td>
<td>0.0955</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative Range 0.40</td>
<td>0.0010</td>
</tr>
<tr>
<td></td>
<td>M3</td>
<td>Mean 4.87</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative Range 0.44</td>
<td>0.45</td>
</tr>
<tr>
<td>CBF</td>
<td>M1</td>
<td>Mean 0.09</td>
<td>&gt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative Range 0.45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>Mean 0.10</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative Range 0.37</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>M3</td>
<td>Mean 0.14</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative Range 0.39</td>
<td>0.37</td>
</tr>
<tr>
<td>CBV</td>
<td>M1</td>
<td>Mean 0.57</td>
<td>&gt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative Range 1.02</td>
<td>0.2101</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>Mean 0.49</td>
<td>&gt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative Range 0.54</td>
<td>0.2056</td>
</tr>
<tr>
<td></td>
<td>M3</td>
<td>Mean 0.56</td>
<td>&gt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative Range 0.51</td>
<td>0.2387</td>
</tr>
</tbody>
</table>

*Pairwise comparisons using Wilcoxon test after adjustment for multiple testing were performed if Friedman test revealed significant differences for the data.
scanner with the same protocol and we have no proof that the results for, for example, a 1.5-T scanner or different sequence parameters would have been comparable. We did not study the correlation of perfusion maps with lesion growth or clinical outcomes. This study did not address the topic of the optimal MRI penumbra definition. Rather, we sought a way of improving consistency when measuring perfusion deficits. Before a decision on optimal thresholds of perfusion parameters and correlations with radiological or clinical outcomes can be made, a high degree of reproducibility has to be achieved. Our analyses revealed that AIFs derived from M3 are associated with less uncertainty. For illustration, see Figure 3. Therefore, future trials identifying optimal perfusion parameters in terms of correlations with meaningful outcomes should use distal rather than proximal MCA branches for AIFs. At least investigators should not vary AIF selection but rather stipulate one single location for their trials.

Conclusion
The level of AIF selection in the MCA has a major impact on reliability and even quantitative parameters of perfusion maps. For better comparison of perfusion maps, the AIF should be defined by selection of distal branches of the MCA contralateral to the suspected ischemia. In future trials involving perfusion imaging, the MCA segment used for the AIF should be specified. These trials should determine the consistency as well as the predictive validity of the AIF from different locations and correlate the results with lesion growth and clinical outcome.

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Disclosures
None.

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