Quantitative Analysis of Hypoperfusion in Acute Stroke
Arterial Spin Labeling Versus Dynamic Susceptibility Contrast

Kambiz Nael, MD; Arash Meshksar, MD; David S. Liebeskind, MD; Bruce M. Coull, MD; Elizabeth A. Krupinski, PhD; J. Pablo Villablanca, MD

Background and Purpose—This study compares the concordance between arterial spin labeling (ASL) and dynamic susceptibility contrast (DSC) for the identification of regional hypoperfusion and diffusion-perfusion mismatch tissue classification using a quantitative method.

Methods—The inclusion criteria for this retrospective study were as follows: patients with acute ischemic syndrome with symptom onset <24 hours and acquisition of both ASL and DSC MR perfusion. The volumes of infarction and hypoperfused lesions were calculated on ASL and DSC multi-parametric maps. Patients were classified into reperfused, matched, or mismatch groups using time to maximum >6 sec as the reference. In a subset of patients who were successfully recanalized, the identical analysis was performed and the infarction and hypoperfused lesion volumes were used for paired pre- and posttreatment comparisons.

Results—Forty-one patients met our inclusion criteria. Twenty patients underwent successful endovascular revascularization (TICI>2a), resulting in a total of 61 ASL-DSC data pairs for comparison. The hypoperfusion volume on ASL-cerebral blood flow best approximated the DSC-time to peak volume (r=0.83) in pretreatment group and time to maximum (r=0.46) after recanalization. Both ASL-cerebral blood flow and DSC-TTP overestimated the hypoperfusion volume compared with time to maximum volume in pretreatment (F=27.41, P<0.0001) and recanalized patients (F=8.78, P<0.0001).

Conclusions—ASL-cerebral blood flow overestimates the DSC time to maximum hypoperfusion volume and mismatch classification in patients with acute ischemic syndrome. Continued overestimation of hypoperfused volume after recanalization suggests flow pattern and velocity changes in addition to arterial transit delay can affects the performance of ASL. (Stroke. 2013;44:3090-3096.)

Key Words: ASL ■ cerebral revascularization ■ perfusion-weighted MRI ■ reperfusion ■ stroke

The optimal method of diagnosis and management of patients with acute ischemic syndrome (AIS) has been a dynamic process during the past decade. MRI with diffusion-weighted imaging (DWI) is highly sensitive and specific for detection of irreversibly damaged brain in acute ischemic stroke. MR perfusion imaging has been useful in the identification of potentially salvageable tissue to determine the best treatment strategy. Although the concept of perfusion-diffusion mismatch remains controversial, it has been used with some success to identify patients who may respond favorably to revascularization therapies in several clinical trials.

Faster image acquisition combined with higher signal-to-noise ratio (SNR) resulting from the use of gadolinium contrast agents has helped dynamic susceptibility contrast (DSC) perfusion become a more robust and widely accepted technique to identify the presence of perfusion abnormalities in patients with AIS. In contrast, arterial spin labeling (ASL) perfusion uses blood as an endogenous contrast agent and does not require gadolinium-based contrast agents. Until recently, the use of ASL techniques in the acute setting had been hampered by a low inherent SNR and longer required acquisition times. Recently, improvement in SNR of the ASL sequence through the incorporation of pseudocontinuous labeling schemes and the use of multicoint technology has significantly improved the efficiency of ASL techniques. As a result of these technical advances and with recent concerns about gadolinium-induced nephrogenic systemic fibrosis in patients with poor renal function, interest in ASL has increased for the evaluation of AIS in acute settings. Several recent studies have shown that ASL can detect hypoperfusion and perfusion-diffusion mismatch in the setting of acute stroke, with variable correlation when compared with DSC imaging ranging from good to modest. It is important to establish how ASL performs in relation to DSC for accurate identification of tissue hypoperfusion.
and the presence of tissue mismatch before it can be used in broad clinical settings and stroke clinical trials.

In this study, we performed a quantitative analysis of hypoperfusion volume and perfusion-diffusion mismatch ratios in patients with AIS to determine how ASL-cerebral blood flow (CBF) performs against multiparametric DSC perfusion, including time to peak (TTP), CBF, and time to maximum (Tmax). We also evaluated the performance of these 2 techniques in a subset of AIS patients before and after successful recanalization.

Methods

Patients

This retrospective single institutional study was performed with institutional review board (IRB) approval. Electronic medical records of patients with suspected AIS form September 2010 to August 2012 were reviewed. Inclusion criteria included the following: (1) interval between the onset of neurological deficits to MRI of less than 24 hours; (2) presence of infarction as identified by restricted diffusion; and (3) both DSC and ASL studies were obtained. In patients with successful recanalization, postprocedural DSC, and ASL studies were also evaluated.

Patient demographic data, median time from last known well to first MRI, baseline National Institutes of Health Stroke Scale scores (NIHSS), number of patients achieving recanalization, the extent of recanalization using postprocedure angiography and the TICI scoring method,15 and the type of scanner used (3.0 or 1.5T) were documented for each patient.

Imaging Protocol

All patients underwent MRI on either a 1.5T (Siemens Avanto; Erlangen, Germany) or 3.0T (Siemens Trio; Erlangen, Germany) MR system. The imaging protocol included DWI, fluid attenuation inversion recovery imaging (FLAIR), gradient recalled echo (GRE), MR angiography, DSC, and ASL perfusion imaging.

DSC images were acquired using a gradient-echo echoplanar imaging (EPI) sequence with the following parameters: TR, 1800/2500 ms for 3.0T/1.5T; TE, 30/45 ms for 3.0T/1.5T; field of view, 22 cm; matrix size, 128 × 128, 26 × 5 mm slices. A GRAPPA factor of 2 was used for parallel acquisition resulting in a 2-minute scan time. During dynamic acquisition, a single dose of 0.1 mmol/kg of gadolinium contrast agent was injected at a rate of 5 mL/s. ASL was performed using a pseudocontinuous pulse sequence with background suppression using a 3D GRASE (gradient and spin echo) readout with the following parameters: TR/TE/label time/postlabel delay, 4000/22/1500/2000 ms; field of view, 22 cm; matrix size, 64 × 64, 26 × 5 mm slices; GRAPPA factor of 2. A total of 30 pairs of tag and control images were obtained in ≈ 4 minutes. A similar acquisition scheme has been used in other quantitative pseudocontinuous investigations.

Data Analysis

Image Post-Processing

ASL image analysis was performed in house using the Interactive Data Language (IDL, Boulder, CO) software program. ASL images were corrected for motion. Pairwise subtraction between label and control images was obtained and averaged to generate the mean difference image. The ASL-CBF maps were calculated based on a previously published model6 (see online-only Data Supplement).

DSC images were processed using a commercially available FDA-approved software (Olea Sphere, Medical SAS, France). DSC analysis consisted of the following steps: (1) truncation of the first 5 time points in the DSC time series, because the MR signal does not reach steady state before this time, (2) calculation of prebolus signal intensity on a voxel-wise basis, and then (3) conversion of truncated DSC time series to a concentration-time curve based on the T2* relativity of the contrast agent. The arterial input function was selected automatically and multi-parametric perfusion maps including CBF, TTP, and Tmax were then calculated using a block-circulant singular value decomposition technique.14

Quantitative Image Evaluation

DWI, apparent diffusion coefficient, DSC, and ASL images for each patient were coregistered with the Olea software using a 12 degree of freedom transformation and a mutual information cost function. This was followed by visual inspection to ensure adequate alignment. The volume of the infarction core was automatically calculated by the software using threshold method defined as an apparent diffusion coefficient value less than 600 × 10−6 mm2/s.15,16 Likewise, the volume of hypoperfusion defined as Tmax >6 seconds17,18 was automatically calculated and used as the standard of reference.

Subsequently, the volume of hypoperfusion on DSC-TTP, DSC-CBF, and ASL-CBF was calculated using a voxel based signal intensity threshold method. A perfusion deficit was defined as an area with visually perceptible increased TTP and decreased CBF on DSC maps, and with decreased perfusion signal on ASL-CBF when compared with the surrounding brain tissue and the homologous contralateral hemisphere. When a hypoperfusion deficit was identified, a 3D volumetric region of interest was created based on the signal intensity subsuming the entire region of hypoperfusion and the volume of hypoperfusion was calculated. The range included was the interval of pixel values to include from the central value of the initial seed voxel. Manual restriction of the regions of interest was applied when necessary. The same process was repeated on the postrecanalization scans to determine the volume of the infarction core, Tmax >6 sec hypoperfusion, and perfusion deficits on DSC-TTP, DSC-CBF, and ASL-CBF.

In addition, the mismatch ratios for Tmax, TTP, CBF, and ASL-CBF were calculated for each patient by dividing the hypoperfusion volume by the infarction core volume. Using the modified Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) criteria,19 the patients were categorized into 3 groups: (1) mismatch, perfusion abnormality volume >180% of infarction core volume; (2) matched, perfusion abnormality volume >70% but <180% of the infarction core volume; and (3) reperfused, perfusion abnormality volume <70% of the infarction core volume. These scores were then used to perform comparative analysis between perfusion parameters using Tmax as the reference.

Statistical Analysis

Statistical analyses were performed using MedCalc (version 12.2.1, MedCalc Software, Belgium). The quantitative volumetric data were plotted as mean and SD (standard deviation) and tested for statistical significance using a repeated measure ANOVA (Analysis of Variance). Correlation coefficients between volumetric data from DSC-TTP, DSC-CBF, and ASL-CBF were calculated against Tmax >6 sec using regression analysis with 95% confidence intervals (CI). The Spearman Rank correlation with 95% CI was calculated to evaluate the intermodality correlation for perfusion-diffusion mismatch classification, again using Tmax as the reference. The significance of quantitative value changes before and after revascularization was tested by using a 2-tailed paired t test on both the ASL-CBF and DSC perfusion parameters. Finally, the differences between the quantitative values between 1.5 and 3.0T MR magnet strengths were tested for statistical significance. The significance level was defined as P<0.05.

Results

A total of 41 patients (26 M, 15 F) with a mean age of 60.1 years (range, 19–84) met our inclusion criteria. Twenty patients who were successfully recanalized were also imaged after reperfusion, resulting in a total of 61 pairs of DSC-ASL for quantitative analysis. Thirty-eight (92%) patients had evidence of large arterial steno-occlusive disease on MRA
including (1) carotid-T occlusion (n=9); (2) M1 occlusion (n=16); (3) M2 occlusion (n=9); and (4) occlusive carotid dissection (n=4). Three patients had occlusion of distal sylvian MCA branches. Of 28 patients who underwent therapeutic intervention, 20 patients (71%) achieved adequate recanalization (TICI ≥2a) confirmed by postprocedural angiography (TICI 3, n=6; TICI 2b, n=9; and TICI 2a, n=5). The therapeutic procedures for these patients included the following: (1) mechanical clot retrieval (n=18); (2) intra-arterial tPA (n=6); and (3) stent placement for carotid dissection (n=4).

NIHSS scores at baseline ranged from 3 to 27 with a median of 17. The median time from last well known to first MRI was 5.5 hours (range: 1–11 hours). The median time from first MRI to groin puncture was 68 minutes (range: 25–320 minutes). Thirty-seven studies were performed on 3.0T and twenty-four on the 1.5 T MR scanner.

The mean±SD of the infarction core (apparent diffusion coefficient < 600 × 10−6 mm2/s) volume was 19.3±21 mL. The mean±SD of the hypoperfusion volumes were 157.5±75 mL DSC-Tmax, 206.5±69 mL for DSC-TTP, 47.1±39 mL for DSC-CBF, and 214±93 mL for ASL-CBF, respectively.

The hypoperfusion volumes on ASL-CBF were not statistically significant different from the volumes calculated on DSC-TTP (P=0.68). However, they were significantly larger than the volumes obtained based on DSC-CBF and Tmax (F=8.78, P<0.005). The average decrease in hypoperfusion volume decreased after revascularization on all perfusion parameters (F=8.78, P<0.0001). The correlation coefficients for hypoperfusion volumes calculated using ASL-CBF and Tmax (F=27.41, P<0.0001; Figure 1). The correlation coefficients for hypoperfusion volumes calculated using ASL-CBF as compared with DSC TTP, Tmax, and CBF were r=0.83, r=0.76, and r=0.34, respectively. The bivariate scattergram plots with 95%CI shown in Figure 2. The correlation between quantitative perfusion-diffusion mismatch ratios using DEFUSE criteria19 is presented in Table 1. Using Tmax >6 sec as the reference, DSC-TTP and ASL-CBF overestimated the mismatch in 2 patients (5%), whereas DSC-CBF underestimated the mismatch in 11 patients (26%).

The mean±SD for hypoperfusion volumes based on magnetic field strength were as follows: for DSC-CBF, 53±33 mL (1.5T), 35±21 mL (3T); for DSC-TTP, 201±82 mL (1.5T), 209±47 mL (3T); for DSC-Tmax, 140±84 mL (1.5T), 168±50 mL (3T); and for ASL-CBF, 226±74 mL (1.5T), 183±56 mL (3T). There was no difference between the TTP and Tmax hypoperfusion volumes at 1.5 versus 3T (P=0.6 and 0.3, respectively). The hypoperfusion volume was higher on both ASL-CBF and DSC-CBF at 1.5T compared with 3T, although the difference did not reach statistical significance (P=0.07 and 0.05, respectively).

**Revascularized Group**

The mean±SD of the infarction core (apparent diffusion coefficient < 600 × 10−6 mm2/s) volume was 21±24 mL. The mean±SD of the hypoperfusion volume were 32±24 mL for DSC-Tmax, 51.1±40 mL for DSC-TTP, 13.2±11.8 mL for DSC-CBF, and 53.8±48 mL for ASL-CBF. Similar to pre-treatment group, no statistically significant difference was found between the hypoperfusion volumes measured on ASL-CBF and TTP (P=0.8). However, they remained significantly larger than volumes measured on DSC-CBF and Tmax (F=8.78, P<0.0001). Hypoperfusion volume was significantly decreased after revascularization on all perfusion parameters (P<0.005). The average decrease in hypoperfusion volume was 122.8 mL for Tmax, 169.5 mL for TTP, 183.2 for ASL-CBF, and 19.8 for CBF (Figure 3).

The correlation coefficients for hypoperfusion volumes calculated on ASL-CBF against DSC TTP, Tmax, and CBF were r=0.28, r=0.46, and r=0.35, respectively, indicating a poor correlation. The bivariate scattergram plots with 95% CI for these correlations are shown in Figure 2.

In the successfully recanalized group (TICI ≥2a) based on postprocedural angiography, using DEFUSE criteria and a Tmax >6 sec as the standard of reference, 12/18 patients (60%) demonstrated reperfusion, whereas 8/18 (40%) patients showed persistent perfusion-diffusion mismatch (Table 2). Table 2 shows the correlation between perfusion parameters for classification of perfusion-diffusion mismatch using DEFUSE criteria in recanalized patients. DSC-TTP and ASL-CBF overestimated the perfusion-diffusion mismatch in 3 (15%) and 5 (25%) patients, respectively, whereas DSC-CBF underestimated the mismatch in 8 patients (40%), compared with Tmax >6 sec as the reference of standard.

The mean of infarct growth in revascularized patient was 7.2 mL, which was not statistically significant (P=0.06). The correlation between the change in the hypoperfusion volume...
and the infarction growth was $r=0.41, 0.49, 0.69$ for DSC-Tmax, TTP, and CBF, respectively and $r=0.20$ for ASL-CBF.

### Discussion

In this study, we compared a quantitative analysis of hypoperfusion as measured by ASL-CBF against multiparametric DSC in patients with AIS, and in a subset of patients who underwent successful recanalization. In addition, we measured the correlation between these perfusion parameters for the determination of clinically relevant perfusion-diffusion mismatch classification and compared the results with a Tmax >6 sec as the standard of reference as reported in several recent studies.5,11,17 We note 4 primary findings:

The first is that hypoperfusion volume on ASL-CBF correlated best with DSC-TTP ($r=0.83$) in patients with AIS. When compared with Tmax, both ASL-CBF and DSC-TTP overestimated the region of hypoperfusion by $\approx 30\%$, and the mismatch classification in 5% of patients. Some of the discrepancy between ASL-CBF and DSC perfusion imaging may stem from the fact that these techniques measure different perfusion parameters. The high correlation between ASL-CBF and DSC-TTP maps for hypoperfusion volumes suggests that measures of ASL-CBF may reflect both delayed transit and reduced CBF effects, which are manifested as prolonged TTP on DSC. This is consistent with the prior reports in the literature indicating good correlation between ASL-CBF and DSC-TTP, in particular when major transit delays are present.20,21 Based on our findings, it is fair to conclude that ASL-CBF and unthresholded DSC-TTP may have a similar diagnostic performance for detection of hypoperfusion volume and mismatch classification.

The ability to use a predefined threshold is required for wide clinical acceptance and reproducibility of a particular perfusion parameter across stroke centers. In addition, using thresholds enable the clinicians to differentiate variable stages of hemodynamic spectrum from benign oligemia to ischemia to infarction. For example, to exclude benign oligemia, the Tmax has evolved from a threshold of $>2$ seconds3,4 to $>6$ seconds.5,17 One of the main limitations of ASL at its current stage is the inability to use a predefined threshold because of insufficient signal to noise and signal gradient across the ASL-CBF maps. A perfusion deficit on ASL-CBF may represent any part of hemodynamic spectrum including benign oligemia, hypoperfusion, or delayed perfusion and likely a combination of all of the above. An inability to apply a threshold makes it difficult to separate these different hemodynamic states from each other.

Our results also suggest that ASL-CBF, as currently designed, may be overly sensitive to arterial transient delays. This remains a substantial obstacle to quantification and to the

### Table 1. Perfusion-Diffusion Mismatch Classification Using DEFUSE Criteria (n=41)

<table>
<thead>
<tr>
<th>Mismatch Classification</th>
<th>DSC-Tmax</th>
<th>DSC-TTP</th>
<th>DSC-CBF</th>
<th>ASL-CBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reperfused</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Matched</td>
<td>2</td>
<td>0</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Mismatched</td>
<td>39</td>
<td>41</td>
<td>28</td>
<td>41</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>41</td>
<td>41</td>
<td>41</td>
</tr>
</tbody>
</table>

Perfusion-diffusion ratio was $<0.7$, $0.7\leq1.8$, and $\geq1.8$ for reperfused, matched, and mismatched patients, respectively. Spearman Rank correlations + 95% confidence interval for the mismatch classification were $r=0.88$, $0.79–0.94$ for ASL-CBF vs Tmax; $r=0.92$, $0.84–0.95$ for ASL-CBF vs TTP; and $r=0.20$, 0.1–0.48 for ASL-CBF vs CBF. ASL indicates arterial spin labeling; CBF, cerebral blood flow; DSC, dynamic susceptibility contrast; Tmax, time to maximum; and TTP, time to peak.

![Figure 2](http://stroke.ahajournals.org/) The bivariate scattergram plots with 95% confidence interval for correlation of hypoperfused volume on ASL-CBF, DSC-Tmax, TTP, and CBF before treatment, n=41 (upper row) and after successful recanalization, n=20 (lower row). In pretreatment group, ASL-CBF best correlates with DSC-TTP (correlation coefficients of ASL-CBF against DSC TTP, Tmax, and CBF are $r=0.83$, $r=0.76$, and $r=0.34$, respectively). After recanalization, ASL-CBF best correlates with DSC-Tmax (correlation coefficients of ASL-CBF against DSC TTP, Tmax, and CBF are $r=0.28$, $r=0.46$, and $r=0.35$, respectively). ASL indicates arterial spin labeling; CBF, cerebral blood flow; DSC, dynamic susceptibility contrast; Tmax, time to maximum; and TTP, time to peak.
adoption of ASL in clinical practice. Although the sensitivity to arterial transit delays in ASL perfusion can be minimized by using a longer postlabeling delay, the sensitivity is subsequently reduced because of the T1 relaxation of blood during this period. Transitioning to a higher field strength may partially mitigate this limitation, because T1 increases with field strength. The use of ASL techniques with varying postlabeling delays to fit the data separately to transit time and perfusion deficit may also provide more satisfactory results. However, ASL using variable postlabeling delays requires longer acquisition times and results in a lower SNR, limiting their use in the acute clinical setting.

Our second finding is that in recanalized patients, quantitative hypoperfusion volume on ASL-CBF correlated rather weakly with Tmax. We anticipated that because delayed arterial transit has been minimized by recanlization, the hypoperfusion volume on ASL-CBF should approximate Tmax. However, we noted an overall lower correlation between the hypoperfused volume measured on ASL-CBF and DSC parameters in the recanalized patients, and ASL continued to significantly overestimate the hypoperfusion by volume and mismatch classification in 25% of patients when compared to Tmax. At least part of this may be explained by the presence of more heterogeneous and complex flow patterns in recanalized patients. One of the most critical parameters of the pCASL method that could affect perfusion quantification and the quality of perfusion images is the labeling efficiency, α, defined as (arterial blood in the control scan – arterial blood in the label scan)/2 (see online-only Data Supplement). The labeling process of pCASL is not strictly an adiabatic inversion. Therefore, the labeling efficiency can be affected by B₀ inhomogeneity, B₁ inhomogeneity, and flow velocity. As shown by Aslan et al, even modest changes in flow velocity within brain arteries in response to hypercapnia can result in a reduction in the labeling efficiency, which in turn may impact the precision of CBF measurements. As expected, these inaccuracies can be magnified several-fold by hemodynamic changes occurring following recanalization of a major cerebral artery such as the internal carotid or proximal middle cerebral arteries, as recently shown. The general kinetic model for accurate assessment of CBF using ASL assumes a complete exchange of labeled blood and tissue spins. This complete exchange may not occur in patients after recanalization of major arteries, where rapid blood flow rates and luxury

<table>
<thead>
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<th>Mismatch Classification</th>
<th>DSC-Tmax</th>
<th>DSC-TTP</th>
<th>DSC-CBF</th>
<th>ASL-CBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reperefused</td>
<td>5</td>
<td>5</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Matched</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Mismatched</td>
<td>8</td>
<td>11</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>20</td>
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</tr>
</tbody>
</table>

Perfusion-diffusion ratio was <0.7, 0.7≤1.8, and ≥1.8 for reperefused, matched, and mismatched patients, respectively. Spearman Rank correlations + 95% confidence interval for the mismatch classification were = -0.44, 0.1–0.74 for ASL-CBF vs Tmax; = -0.46, 0.2–0.75 for ASL-CBF vs TTP, and = -0.42, 0.1–0.70 for ASL-CBF vs CBF. ASL indicates arterial spin labeling; CBF, cerebral blood flow; DSC, dynamic susceptibility contrast; Tmax, time to maximum; and TTP, time to peak.
perfusion can negatively impact the performance of ASL.\textsuperscript{28} One solution may be to use different pre- and posttreatment ASL postlabeling delay times to account for the effects of the arterial occlusion and recanalization. Velocity-selective ASL,\textsuperscript{29} which is theoretically insensitive to arrival time, may also help to address some of these limitations, although its efficacy in patients with AIS has yet to be established.

The third finding was that of a major discrepancy for the determination of reperfusion between MR perfusion parameters and cerebral angiography. In 20 patients who achieved successful recanalization defined by postprocedural angiography with TICI >2A score, our MR perfusion parameters using DEFUSE criteria identified reperfusion in 60%, 45%, and 85% using DSC-Tmax, TTP, and CBF, respectively, and 35% using ASL-CBF.

Finally, our results suggest that the hypoperfusion volume on DSC-CBF most closely approximates the DWI infarct volume. We found DSC-CBF to be the most specific parametric measure for the prediction of infarction growth ($r=0.69$). This comes at a cost of a decreased sensitivity for hypoperfusion volume based on DSC-CBF as compared with ASL-CBF and DSC time-based parameters (Tmax, TTP). As a result, DSC-CBF underestimated mismatch classification in 26% of AIS patients before treatment and in 40% of recanalized patients when using Tmax >6 sec as the standard of reference. Consequently, DSC-CBF should be interpreted with caution and may not be optimally suited for mismatch algorithms currently in use, such as DEFUSE. One of the main limitations of DSC-CBF for the evaluation of hypoperfusion volume is the inherently lower CBF values of white matter as compared to cerebral cortex, which can be exaggerated even further in the setting stroke and proximal arterial occlusion, resulting in further variability. This perhaps explains the reason that DSC-CBF has not been implemented widely in the setting of clinical trials to determine the mismatch classification.

This study has several limitations, including (1) a relatively small sample size drawn from a single institution possibly introducing a sample bias, (2) high frequency of mismatch ratios in our study population is likely related to the inclusion of a large number of patients with proximal arterial occlusion, (3) a retrospective study design, possibly introducing an unknown patient selection bias, (4) although the volumetric analysis of infarction and Tmax hypoperfusion was performed using a threshold, the volume on DSC-TTP and CBF, and ASL-CBF was measured without a predefined numeric threshold and was based on visualization of hypoperfusion alone, which can introduce some variability into the analysis. In addition, DSC was assumed to be the comparative standard, possibly introducing a modality specific bias, and (5) finally, the choice of a longer TR in our DSC sequence at 1.5T is less ideal for DSC perfusion. This value was chosen to improve the lower SNR at 1.5T.\textsuperscript{30} It is possible this choice of TR could have resulted in undersampling of the AIF and therefore overestimation of perfusion parameters at 1.5T.

**Conclusions**

The hypoperfusion volume on ASL-CBF correlates best with DSC-TTP. When compared with Tmax, both ASL-CBF and DSC-TTP overestimate the hypoperfusion volume and mismatch classification even after recanalization, suggesting flow pattern and velocity changes in addition to arterial transit delay can affect the performance of ASL. Varying degree post-labeling delay or ASL techniques insensitive to arrival time will likely determine the future of ASL in evaluation of different hemodynamic stages of AIS.

**Disclosures**

None.

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**ASL Analysis:**
ASL images were motion corrected, pairwise subtracted between the tag and control images, and averaged to generate a mean difference image, $\Delta M$.

Quantitative cerebral blood flow ($C_{BF_{ASL}}$) maps were calculated as follow:

$$C_{BF_{ASL}} = \frac{\lambda \cdot \Delta M \cdot R_{1a}}{2 \cdot \alpha \cdot M_0} \left[ e^{-w \cdot R_{1a}} - e^{-(\tau + w) \cdot R_{1a}} \right]$$

where $R_{1a} = 0.72 \text{sec}^{-1}$ (0.61sec$^{-1}$ at 1.5T) is the longitudinal relaxation rate of blood, $M_0$ is the equilibrium magnetization of brain tissue, $\alpha = 0.8$ is the tagging efficiency, $\tau = 1.5 \text{sec}$ is the duration of the labeling pulse, $w = 2 \text{sec}$ is the post-labeling delay time and $\lambda = 0.9 \text{g/ml}$ is blood/tissue water partition coefficient. Note that this equation assumes the labeled blood spins remain primarily in the vasculature rather than exchanging freely with tissue water, an assumption which is justified in patients with stroke with prolonged arterial transit times.