Pseudocontinuous Arterial Spin Labeling Quantifies Relative Cerebral Blood Flow in Acute Stroke

Daymara A. Hernandez, BA; Reinoud P.H. Bokkers, MD, PhD; Raymond V. Mirasol, BA; Marie Luby, PhD; Erica C. Henning, PhD; José G. Merino, MD; Steven Warach, MD, PhD; Lawrence L. Latour, PhD

Background and Purpose—The aim of this study was to test whether arterial spin labeling (ASL) can detect significant differences in relative cerebral blood flow (rCBF) in the core, mismatch, and reverse-mismatch regions, and whether rCBF values measured by ASL in those areas differ from values obtained using dynamic susceptibility contrast (DSC) MRI.

Methods—Acute stroke patients were imaged with diffusion-weighted imaging (DWI) and perfusion-weighted imaging (ASL and DSC) MRI. An expert reader segmented the ischemic lesion on DWI and the DSC time-to-peak (TTP) maps. Three regions were defined: core (DWI+, TTP+), mismatch (DWI−, TTP+), and reverse-mismatch (DWI+, TTP−). For both ASL and DSC, rCBF maps were created with commercially available software, and the ratio was calculated as the mean signal intensity measured on the side of the lesion to that of the homologous region in the contralateral hemisphere. Values obtained from core, mismatch, and reverse-mismatch were used for paired comparison.

Results—Twenty-eight patients were included in the study. The mean age was 65.6 (16.9) years, with a median baseline National Institutes of Health Stroke Scale score of 10 (interquartile range, 4–17). Median time from last known normal to MRI was 5.7 hours (interquartile range, 2.9–22.6). Mean rCBF ratios were significantly higher in the mismatch 0.53 (0.23) versus the core 0.39 (0.33) and reverse-mismatch 0.68 (0.49) versus the core 0.38 (0.35). Differences in rCBF measured with DSC and ASL were not significant.

Conclusions—ASL allows for the measurement of rCBF in the core and mismatch regions. Values in the mismatch were significantly higher than in the core, suggesting there is potential salvageable tissue. (Stroke. 2012;43:753-758.)

Key Words: acute stroke • cerebral blood flow • perfusion quantification
routinely to monitor longitudinal changes in cerebral blood flow over time, it is important to demonstrate that it can detect regional differences that correspond to the ischemic lesion at a single time point.

The aim of this study was to test whether ASL could be used to detect significant differences in relative cerebral blood flow (rCBF) in the core, mismatch, and reverse-mismatch regions, and whether rCBF values measured by ASL in those areas differ from values obtained using DSC MRI.

**Patients and Methods**

**Patients**

This is a retrospective analysis that is part of an ongoing quality-improvement process to provide perfusion imaging to patients in renal failure. The data collection and analysis were performed in compliance with the National Institutes of Health and study site institutional ethics requirements. Patients were included in this study if they had a baseline MRI with interpretable baseline ASL and DSC, a detectable perfusion deficit on ASL as identified by 2 stroke neurologists blinded to patient information, and a discharge diagnosis of ischemic stroke. If at the time of the initial evaluation the patients were eligible for treatment with standard intravenous tissue-type plasminogen activator, then the baseline MRI had to be completed within 4.5 hours from the time last known well and before any acute treatment was started. Patients were excluded if they had a carotid occlusion, a posterior circulation infarct, or if they were unable to have a DSC study because their Glomerular Filtration Rate (GFR) was <30 mL/min per 1.73 m².

**Imaging**

All patients were imaged on a clinical 3 Tesla (T) MRI scanner (Achieva; Philips Medical Systems) equipped with an 8-channel coil and locally developed ASL perfusion imaging software. Imaging was performed as part of the standard baseline evaluation of acute stroke and included DWI, ASL, and DSC perfusion imaging. ASL perfusion imaging was performed with a pseudocontinuous labeling sequence according to a previously published protocol. The parameters of the pseudocontinuous ASL sequence were: 2.5 minutes in duration; 3 × 3 × 7-mm resolution; repetition time/echo time (TR/TE) = 4000/14 ms; pairs of control/label 12; 20 slices with a 7.0-mm thickness with whole brain coverage; and background suppression that allows the reduction of acquisition time while improving the signal-to-noise ratio. DSC and DWI were acquired with the vendor’s standard commercially available sequences. The parameters for the DSC sequence were: 1.7 minutes in duration; 3 × 3 × 7-mm resolution; gradient echo sequence with a TR/TE 1000/25 ms; and 20 slices with a slice thickness of 7.0 mm with a single dose of gadolinium at 5 mL. The parameters for the DWI sequence were: 3.0 minutes in duration; diffusion tensor acquisition 15-direction with postacquisition registration before calculation of the trace-weighted DWI; TR/TE 4500/62.1 ms; SENSE factor 1.75; field of view (FOV) 240 × 240 mm; and 40 slices with a continuous slice thickness of 3.5 mm.

ASL-CBF perfusion maps were calculated from the labeled and unlabeled ASL images with Matlab (The MathWorks, Mass, version 7.5) according to a previously published model. The T2* transverse relaxation rate and T1 of arterial blood at 3 T were assumed to be 50 ms and 1680 ms, respectively. The water content of blood was assumed to be 0.76%. The labeling efficiency was assumed to be 85% based on numeric simulations of the labeling process, comparable to simulations by Wu et al.

DSC time-to-peak (TTP) maps were calculated from the DSC sequences with the vendor’s standard perfusion software (Advanced Brain Perfusion, Philips Healthcare) on the MRI console. DSC-CBF perfusion maps were generated in Perfspace (Olema Medical). Automated noise reduction was applied to the perfusion images. An automatic arterial input function was produced by sampling multiple points, not including the hypoperfused area. The mean arterial input function was used along with circular deconvolution. The upper limit threshold of the intensity values was reduced to 30 000 from 32 000 with the commercially available imaging analysis software (MIPAV Medical Image Processing, Analysis, and Visualization, version 4.4; National Institutes of Health) for multiple cases.

**Qualitative Image Analysis**

Two experienced stroke neurologists blinded to clinical information read the images. Each reader assessed each DWI, ASL-CBF, and DSC-TTP by itself in random order to determine the presence of a lesion on DWI and a perfusion deficit on ASL-CBF and DSC-TTP. In addition, they rated image quality as excellent, good, fair, poor, and uninterpretable. A consensus reading was held for disagreements about the presence of perfusion deficits on ASL-CBF. The readers used commercially available software to view the images (MIPAV) and were able to adjust for contrast, color scheme, and size.

**Quantitative Image Analysis**

DWI and DSC-TTP were used to identify the areas of the core (the area where there is diffusion and perfusion deficit [DWI+, TTP+]), mismatch (the area where there is perfusion but no diffusion deficit [DWI–, TTP+]), and reverse-mismatch (the area where there is diffusion but no perfusion deficit [DWI+, TTP–]). The images were coregistered using the following parameters: optimized automatic registration; 6 rigid degrees of freedom; trilinear interpolation; and a correlation ratio cost function. DWI sequences were resampled to the slice thickness of the DSC-TTP and ASL to colocalize them to 20 slices. Midsagittal alignment was performed on trace-weighted DWI and used to coregister DSC-TTP, DSC-CBF, and ASL-CBF series data.

After coregistration, an expert reader segmented the ischemic lesion on DWI and the perfusion deficit on DSC-TTP. These areas were overlapped to create 3 volumes of interest (VOI): core, mismatch, and reverse-mismatch (Figure 1). Once combined, the 3 VOIs were converted to binary masks to generate the ipsilateral mask. To generate the contralateral mask, the ipsilateral was cloned and mirrored across midline into the contralateral hemisphere to identify a homologous region of healthy tissue as a control. A binary brain mask was generated for each patient DWI to reduce contamination in the perfusion data from signal outside of the brain. Then, the ipsilateral and contralateral masks were combined with the brain mask to remove regions overlapping the ventricles, sulci, or cerebrospinal fluid, resulting in the final mask with 6 subregions. The final mask that contained the 6 subregions (core, mismatch, and reverse-mismatch on both hemispheres) was applied to the final VOIs. After segmentation, ASL-CBF images were reviewed and the presence of hyperintensity in the sulci, suggestive of delayed arrival of the ASL tag in the arteries, was noted.

The final VOIs were copied to the ASL-CBF and DSC-CBF, where the number of voxels, volume, average voxel intensity, standard deviation of intensity, and median intensity were measured. The rCBF was calculated as the ratio of the mean signal intensity measured on the side of the lesion to that of the homologous region in the contralateral hemisphere. Because small volumes are prone to measurement error, the quantitative analysis was limited to patients who had core, reverse-mismatch, and mismatch volumes ≥2 mL.

**Statistical Analysis**

SPSS (SPSS version 18.0.0) was used for all statistical analyses. Patient demographics and signal intensity values were analyzed with the descriptive statistical analysis tool. Mismatch, reverse-mismatch, and core VOIs ≥2 mL were used for comparisons among the subregions in ASL and DSC. To determine if the rCBF measured by ASL in the core, mismatch, and reverse-mismatch differ from the values obtained using DSC, the Wilcoxon signed-rank test and paired sample t test were used. All P < 0.05 were considered statistically significant. The values are expressed as mean (standard deviation) and median (interquartile range) according to the normality distribution values of the Kolmogorov-Smirnov.
Results

Over the 7 months of the study (June 2009–January 2010), 105 consecutive patients had a baseline MRI that included ASL and DSC sequences, and 28 met the inclusion and exclusion criteria. The mean age was 65.6 (16.9) years, 15 were women, and the median baseline National Institutes of Health Stroke Scale score was 10 (interquartile range, 4–17). The median time from last seen normal to MRI was 5.7 hours (interquartile range, 2.9–22.6). Eleven patients (39%) were treated with intravenous tissue-type plasminogen activator; in these patients, the median baseline National Institutes of Health Stroke Scale score was 11 (interquartile range, 4–15.5) and the median time from last seen normal to baseline MRI was 2.3 hours (interquartile range, 2.1–3.7).

The quality of the ASL-CBF and DSC-TTP images varied. Of the ASL-CBF, 82.1% were good to excellent, 7.1% were fair, and 10.7% were of poor quality. The respective values for the DSC-TTP were 78.6%, 7.1%, and 14.3%. Intraluminal high intensity was observed in 15 patients, seen in regions of reverse-mismatch in 2, in mismatch in 12, and in core in 1.

The Table shows the median diffusion and perfusion lesion volumes on DWI and DSC-TTP maps. Regions of mismatch were found in all 28 patients, core regions were found in 25, and reverse-mismatch was found in 26. The median volumes on ASL for the ipsilateral hemisphere are: reverse-mismatch, 2.4 mL; mismatch, 42.1 mL; and core, 6.0 mL. A total of 23 patients were included in the core and mismatch, 17 patients in the core and reverse-mismatch, and 18 patients in the mismatch and reverse-mismatch analyses for core and mismatch, core and reverse-mismatch, and mismatch and reverse-mismatch ≥2 mL, respectively.

The rCBF ratios using ASL and DSC are shown in Figure 2 and Figure 3. In the core/mismatch analysis, using ASL the rCBF ratio was 0.39 (SD, 0.33) in the area of the core and 0.53 (SD, 0.23) in the area of mismatch (P=0.023; mean difference, 14.2%; 95% CI, 0.02–0.26). Using DSC, the CBF...
ratio was 0.4 (SD, 0.21) in the core and 0.63 (SD, 0.18) in the region of mismatch (P=0.001; mean difference, 24.4%; 95% CI, 0.11–0.38).

In the mismatch/reverse-mismatch analysis, using ASL the rCBF ratio was 0.51 (SD, 0.19) in the area of the mismatch and 0.71 (SD, 0.54) in the area of reverse-mismatch (P=0.155; mean difference, 20.5%; 95% CI, 0.16–0.31). Using DSC, the CBF ratio was 0.64 (SD, 0.34) in the mismatch and 0.64 (SD, 0.34) in the region of reverse-mismatch (P=0.971; mean difference, 0.3%; 95% CI, 0.18 to 0.19).

For the 28 patients studied, no significant difference could be detected between rCBF values obtained using ASL and those obtained using DSC in all subregions, core (P=0.545), mismatch (P=0.711), and reverse-mismatch (P=0.620).

Discussion
This study is the first to our knowledge to demonstrate that the ischemic core and areas of mismatch and reverse-mismatch can be differentiated quantitatively with ASL using rCBF values obtained during a baseline routine clinical MRI study that includes a 2.5-minute pseudocontinuous ASL sequence. Our findings suggest that ASL may be used to quantify areas of salvageable tissue and to dynamically monitor regional blood flow responses to a therapeutic intervention. Because ASL does not require the use of an exogenous contrast agent and compliments DWI and DSC MRI, it may be used to repeatedly image acute stroke patients to learn more about stroke pathophysiology and evaluate new treatments.

Validation studies addressing CBF quantification have previously compared ASL to positron emission tomography, SPECT, and DSC in a wide range of neurological and oncological diseases, including stroke. ASL has been compared with DSC to detect perfusion deficits and perfusion/diffusion mismatch in patients with acute stroke. Using a 6-minute continuous labeling sequence, Chalela et al showed that the quantitative regional CBF values were decreased in the affected hemisphere in comparison to the contralateral tissue in 15 ischemic stroke patients imaged within 24 hours of symptom onset, only 1 of whom received intravenous tissue-type plasminogen activator treatment. However, tissue viability depends on the duration of blood flow decline, regional differences in CBF related to collateral flow, and other factors. For ASL to be practical in the acute setting, the imaging protocol must be brief yet allow quantification of CBF to identify regions of potentially salvageable tissue. Furthermore, validation studies about the success rate of ASL have obtained equivalent results to those obtained in this study in which only 10.7% of the images were of poor quality. In this study, we have demonstrated that it is possible to identify regional differences in rCBF values that correspond to core, mismatch, and reverse-mismatch using a brief ASL sequence in patients before and after administration of intravenous tissue-type plasminogen activator.

The effect of reperfusion therapies such as tissue-type plasminogen activator can be monitored with perfusion imaging. Because ASL is a noninvasive perfusion technique that does not use contrast agents, repetitive perfusion mea-

Figure 3. Arterial spin labeling (ASL) and dynamic susceptibility contrast (DSC) relative cerebral blood flow (rCBF) values of the core, reverse-mismatch, and mismatch, respectively. The agreement between ASL and DSC is moderate because of motion artifact, small lesions, misregistration, or random error. There are 4 patients in the reverse-mismatch graph who had a higher rCBF value on ASL than DSC, of whom 1 had a very small volume, 1 had poor image quality, and 2 may have had a misregistration or random error. There is 1 patient in the mismatch graph who showed a higher rCBF value on ASL than DSC because of a very small volume.
measurements may be performed without the limitation of gadolinium clearance or risk of nephrogenic systemic fibrosis in patients with poor renal function. Measuring reperfusion at cumulative clearance or risk of nephrogenic systemic fibrosis in an area of reverse-mismatch may be performed without the limitation of gadolinium clearance or risk of nephrogenic systemic fibrosis. Unfortunately, in comparison to DSC MRI, the perfusion deficit is not as conspicuous on ASL and smaller lesions may be missed (Bokkers RPH et al., unpublished data, 2011). However, ASL can be used in a complimentary fashion to DWI and DSC MRI, as we have shown here. Lesion and mismatch may be best defined using DWI and DSC, with ASL providing the mechanism for quantification of rCBF to assess therapeutic response in repetitive measures.

A potential limitation of this study is that the VOIs were defined on DSC-TTP but used to assess CBF values for both DSC and ASL. Because ASL and DSC are acquired at different times during the examination and later coregistered, a potential exists for misregistration and differences between localization of the perfusion deficits between the 2 acquisition techniques. Our results using the TTP maps for lesion depiction, however, show a close correspondence between both techniques within the depicted perfusion deficits, ie, core and mismatch. Conversely, as a result of the differences between these 2 modalities, the rCBF values of the reverse-mismatch on ASL show a greater range than on DSC, as illustrated in Figure 2. Because reverse-mismatch may represent regions of spontaneous reperfusion and high reactive hyperemia, it is possible to obtain values that exceed a value of unity, as was the case on ASL but not on DSC. Furthermore, the volumes in the reverse-mismatch VOIs were much smaller than those in the areas of mismatch and core; the volume of reverse-mismatch in our patients was approximately one-seventeenth of the mismatch. The regions of reverse-mismatch, therefore, may have greater variability because of a smaller volume of tissue, contributing to the mean values averaged in the VOI. This results in greater susceptibility of the values to random and systematic error attributable to misregistration. A potential solution would be to use a transit time-sensitive ASL imaging technique based on multiple readouts after the labeling bolus; however, it is uncertain with the natural T1 decay of the arterial blood bolus whether these techniques are sensitive to delayed arrival in the flow territory distal to the blockage as blood is recruited through collateral vessels. Additionally, intraluminal high intensity was present in a greater fraction of regions of mismatch versus the reverse-mismatch, possibly attributable to the effects of delayed transit time. This could be attributed to collateral blood flow compensating hypoperfused areas and could lead to artifactualy high rCBF in ASL of those regions.

A second limitation of this study is that ASL is relatively insensitive for measuring white matter perfusion because of the low perfusion signal, which may hamper CBF quantification within the perfusion deficits as defined with DSC-TTP. To minimize this effect, we used an ASL method combining pseudocontinuous ASL labeling pulses, background suppression, and an MRI field strength of 3.0 T, which has been shown to be sensitive for white matter perfusion and perfusion deficits. A third limitation of this study is the sample size, which could have contributed an inability to detect significant differences in rCBF values between ASL and DSC. A fourth limitation of the study is that there were no significant differences between the areas of mismatch and reverse-mismatch. Therefore, even though reverse-mismatch appears normal on TTP, there is still a decrease in rCBF that is almost the same as mismatch, and consequently areas of mismatch may not be much lower than normally appearing tissue.

This study demonstrates that pseudocontinuous ASL can be used to quantify CBF values in the ischemic core and in areas with perfusion/diffusion mismatch in patients with hyperacute stroke. There were no rCBF differences between ASL and DSC MRI. Because ASL is a quick and noninvasive perfusion technique, it potentially may be used in the future to determine patient eligibility for tissue-type plasminogen activator treatment, clinical trial enrollment, and therapy response.

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Disclosures
None.

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Daymara A. Hernandez, BA1; Reinoud P.H. Bokkers, MD, PhD2; Raymond V. Mirasol, BA1,4; Marie Luby, PhD3; Erica C. Henning, PhD1; José G. Merino, MD1,3; Steven Warach, MD, PhD1; Lawrence L. Latour, PhD1

1 Section on Stroke Diagnostics and Therapeutics, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD; 2 Department of Radiology, University Medical Center Utrecht, Utrecht, the Netherlands; 3 Johns Hopkins Community Physicians, Bethesda, MD; and 4 Howard Hughes Medical Institute, National Institutes of Health Research Scholars Program, Bethesda, MD.

Background and Objectives: The purpose of this study was to determine whether ASL could detect a significant difference in relative cerebral blood flow (rCBF) in core, mismatch, and penumbra regions of acute stroke patients. We also sought to determine whether ASL rCBF values were different from DSC rCBF values.

Methods: Acute stroke patients were imaged with DWI and ASL/DSC MRI. The time to maximum intensity (TTP) was determined from DWI and DSC. The ischemic region was segmented by a neuroradiologist and used to define the core (DWI +, TTP +), mismatch (DWI -, TTP +), and penumbra (DWI +, TTP -) regions. Pseudocontinuous arterial spin labeling and DSC images were analyzed using a commercially available software program to calculate rCBF. The ratio of the rCBF in the diseased hemisphere to the same contralateral region was calculated and compared for each region.

Results: We analyzed 28 patients with a mean age of 65.6 ± 16.9 years. The NIHSS score was 10 (median) (range: 4–17). The mean TTP was 5.7 hours (range: 2.9–22.6). Core rCBF was higher than mismatch rCBF (0.39 ± 0.33 vs. 0.53 ± 0.23, respectively). DSC and ASL rCBF values were not statistically different.

Conclusion: ASL can measure rCBF in the core and mismatch regions. The mismatch region rCBF values were higher than the core region values, suggesting a possible salvageable area.