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

The primary therapeutic target in patients with acute ischemic stroke is decreased cerebral perfusion, and these areas can be identified with perfusion-weighted sequence.1 Diffusion-weighted imaging (DWI) is the most sensitive MRI technique for identifying the acute ischemic core.2 When used together, perfusion-weighted imaging (PWI) and DWI can identify brain tissue with hypoperfusion but normal diffusion (ie, there is PWI and DWI mismatch); this tissue is ischemic but potentially salvageable and therefore is a target for reperfusion therapies.3–4 Dynamic susceptibility contrast (DSC) imaging is the MRI perfusion technique most often used in current clinical practice. DSC MRI tracks the passage of a bolus of gadolinium contrast agent through the brain by acquiring a time series of fast T2*-weighted images.5 Because it takes hours to clear the contrast agent, repetitive injections to monitor changes in blood flow in response to therapeutic intervention are technically impractical. In addition, gadolinium is contraindicated in patients with renal insufficiency and there are limits to the amount that can be safely administered.6 Arterial spin labeling (ASL) is a noninvasive alternative for imaging whole brain cerebral perfusion that uses radio-frequency pulses instead of gadolinium to label inflowing arterial blood.7,8 As a complementary method to DWI and DSC MRI, ASL may be used to repetitively and quantitatively monitor changes in cerebral blood flow in regions of ischemic core and mismatch, it can be used to gain new insights into cerebrovascular pathophysiology and the response to therapy.

Recent studies show that ASL depicts perfusion deficits and can qualitatively identify areas of PWI–DWI mismatch comparable to DSC MRI.9–11 Before ASL can be used...
patients were eligible for treatment with standard intravenous tissue-
protection. If at the time of the initial evaluation the patients were eligible for treatment with standard intravenous tissue-
protection (tPA) or conservative measures, they were included in this study. The patients included in this study had a baseline MRI with interpretable baseline ASL and DSC, a detectable perfusion deficit on ASL as identified by 2 stroke neurologists blinded to clinical 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-
protection, 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/A. 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; 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 3T 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 series with the vendor’s standard perfusion software (Advanced Brain Perfusion, Philips Healthcare) on the MRI console. DSC-CBF perfusion maps were generated in Perfscape (Olea Medical). Automated noise reduction was applied to the perfusion images. An automatic arterial input function was produced by sampling multiple points, not including the hyperperfused 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 VOI were converted to binary masks to generate the ipsilateral mask. To generate the contralateral mask, the ipsilateral mask 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 used to coregister the ASL-CBF and DSC-TTP 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.
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

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<table>
<thead>
<tr>
<th>Table. Median Lesion Volumes Median (Interquartile Range)</th>
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<tr>
<td>Median Lesion Volumes (mL)</td>
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<tr>
<td>All Patients (n=28)</td>
</tr>
<tr>
<td>TTP</td>
</tr>
<tr>
<td>DWI</td>
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<tr>
<td>10.8 (2.1–16.2)</td>
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<tr>
<td>tPA Patients (n=11)</td>
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<tr>
<td>12.0 (1.4–21.6)</td>
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<tr>
<td>TTP</td>
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<tr>
<td>55.6 (15.0–133.2)</td>
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<tr>
<td>58.0 (17.1–128.3)</td>
</tr>
<tr>
<td>Core</td>
</tr>
<tr>
<td>7.0 (1.9–21.0)</td>
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<tr>
<td>9.7 (0.9–23.4)</td>
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<tr>
<td>Mismatch</td>
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<tr>
<td>49.8 (12.7–105.8)</td>
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<tr>
<td>49.3 (17.0–113.0)</td>
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<tr>
<td>Reverse-mismatch</td>
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<tr>
<td>2.4 (0.4–6.7)</td>
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<td>2.3 (0.7–6.3)</td>
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DWI indicates diffusion-weighted imaging; tPA, tissue-type plasminogen activator; TTP, time-to-peak.

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** The acute diffusion and perfusion deficits were segmented on diffusion-weighted imaging (DWI) and dynamic susceptibility contrast (DSC) time-to-peak (TTP). The volumes of interest were superimposed to identify the core, mismatch, and reverse-mismatch. The regions of interest were flipped across midline to the contralateral hemisphere to identify a homologous region of healthy tissue as a control (A) DWI+, (B) DSC-TTP+, (C, D) core (green); the area where there is diffusion and perfusion deficit [DWI+, TTP+], mismatch (blue); the area where there is perfusion but no diffusion deficit [DWI−, TTP+], and reverse-mismatch (red); the area where there is diffusion but no perfusion deficit [DWI+, TTP−].

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Arterial spin labeling (ASL) and dynamic susceptibility contrast (DSC) relative cerebral blood flow values of the core vs reverse-mismatch and mismatch, respectively, show a close correspondence. In most part, there is approximately a linear relationship between the two techniques.
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, 23.6%; 95% CI, 0.16–0.31).

In the core/reverse-mismatch analysis, using ASL the rCBF ratio was 0.38 (SD, 0.35) in the area of the core and 0.68 (SD, 0.49) in the area of reverse-mismatch ($P=0.001$; mean difference, 30%; 95% CI, 14.2–45.7%). Using DSC, the CBF ratio was 0.36 (SD, 0.22) in the core and 0.60 (SD, 0.22) in the region of reverse-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, −0.09 to 0.50). Using DSC, the rCBF ratio was 0.64 (SD, 0.18) 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 rCBF 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 rCBF 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 $\pm 10.7\%$ 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-
sures may be performed without the limitation of gadolinium clearance or risk of nephrogenic systemic fibrosis in patients with poor renal function. Measuring reperfusion at consecutive time points could allow us to measure the speed and duration of thrombolytic activity or ischemia progression to broaden our understanding of these hemodynamic processes. 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 hyperperfused areas and could lead to artifactual 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.

**References**


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背景および目的: 本研究の目的は,動脈スピン標識法 (ASL) によってコア領域,ミスマッチ領域,および逆ミスマッチ領域における相対的脳血流量 (rCBF) の有意な差を検出できるかどうか,またこれらの領域で ASL により測定した rCBF 値が DSC (dynamic susceptibility contrast: 通常の灌流画像) 法による MRI で取得した値と異なるかどうかを検証することである。

方法: 拡散強調画像 (DWI) および灌流強調画像 (ASL および DSC) MRI で急性脳卒中患者の画像を撮像した。専門の読影者が DWI および DSC 最高値到達時間 (TTP) マップの虚血性病変をセグメントに分割した。専門の読影者が DWI および DSC 最高値到達時間 (TTP) マップの虚血性病変をセグメントに分割した。コア (DWI+, TTP+), ミスマッチ (DWI-, TTP+), および逆ミスマッチ (DWI+, TTP-) の 3 つの領域を定義した。ASL と DSC の両方が、市販のソフトウェアで rCBF マップを作成し、病変側で測定した平均信号強度の対側半球の相同領域に対する比を計算した。コア、ミスマッチ、および逆ミスマッチ領域から得た値を一対比較に使用した。

結果: 本研究には 28 例の患者を組み入れた。平均年齢は 65.6 ± 16.9 歳であり、ベースラインの NIHSS スコアの中央値は 10 (四分位範囲: 4 ~ 17) であった。緊急の既知の正常時から MRI までの時間の中央値は 5.7 時間 (四分位範囲: 2.9 ~ 22.6) であった。平均 rCBF 比はミスマッチ (0.53 ± 0.23) がコア (0.39 ± 0.33) より有意に高く、逆ミスマッチ (0.68 ± 0.49) がコア (0.38 ± 0.35) より有意に高かった。DSC と ASL で測定した rCBF の差は有意ではなかった。

結論: ASL ではコア領域とミスマッチ領域の rCBF の測定が可能である。ミスマッチ領域の値はコア領域より有意に高かったことから、サルベージ可能な組織の存在が示唆される。

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