2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

Reduced Cerebral Blood Flow in Benign Oligemia Relates to Poor Clinical Outcome in Acute Ischemic Stroke Patients

Zengping Lin, Tianyao Wang, and Yao Li*, *Senior Member, IEEE*

Abstract — **The imaging of cerebral blow flow (CBF) has shown great promise in predicting the tissue outcome or functional outcome of acute ischemic stroke patients. Arterial spin labeling (ASL) provides a noninvasive tool for quantitative CBF measurement and does not require a contrast agent, which makes it an attractive technology for perfusion imaging in clinical settings. Previous studies have shown the feasibility of using ASL for acute stroke imaging and its potential in stroke outcome prediction. However, the relationship between the tissue-level CBF reduction in hypoperfused region and clinical outcome in acute stroke patients remains not well understood. In this study, we obtained the quantitative measurements of CBF in acute ischemic stroke patients (N = 18) using pseudo-continuous ASL (pCASL) perfusion imaging technology. The tissue-level CBF changes were evaluated and their correlations with patient clinical outcome were explored. Our results showed different CBF values between hypoperfused tissues recruited into infarction and those that survived. Moreover, a significant correlation was found specifically between the CBF reduction in benign oligemia area and patient neurological deficit severity. These findings showed the validity of pCASL perfusion imaging in the assessment of tissue-level CBF information in acute stroke. The association of CBF with patient clinical outcome might provide useful insights in early diagnosis of acute stroke patients.**

I. INTRODUCTION

Stroke is the second leading cause of death globally, with over 80% of all are ischemic strokes due to the blockage of blood supply to the brain [1]. During ischemia, the reduction of cerebral blow flow (CBF) and lack of oxygen and glucose supply result in neuronal necrosis if no timely reperfusion is introduced [2]. The imaging of CBF has shown great promise in predicting the tissue outcome or functional outcome of acute ischemic stroke patients [3-7].

The gold standard for CBF imaging is PET, but its clinical applications have been limited owing to the requirement for exogenous tracers [8]. Magnetic resonance imaging (MRI) techniques have developed fast over the past decades with wider availability. Currently, there are two main MR-based CBF imaging techniques: dynamic susceptibility contrast (DSC) perfusion MRI and arterial spin-labeling (ASL) perfusion MRI. DSC-MRI is efficient but requires the administration of an exogenous contrast agent, which might introduce side effects for patients with renal disease [9]. ASL provides a noninvasive tool for CBF measurement, which utilizes arterial blood water as an endogenous tracer by magnetically labeling the water protons in the arterial blood [10]. Because it does not require a contrast agent, ASL could be easily repeated under different physiological conditions. Moreover, the improved data acquisition and postprocessing of ASL perfusion imaging have significantly increased its clinical applications in stroke studies.

Wang et al. demonstrated the feasibility of using ASL for acute stroke imaging and found a significant correlation between the CBF values measured by pseudo-continuous ASL (pCASL) and DSC in the infarct region of acute stroke patients [11]. Harston et al. found a significant difference in CBF value between ischemic core and infarct growth area in acute stroke patients [12]. Recently, the absolute CBF value quantified using ASL has shown great potentials in stroke outcome prediction [13]. However, the relationship between the tissue-level CBF reduction in hypoperfused region and patient clinical outcome was not well understood, which is of great importance for therapeutic decision making.

In this study, we obtained the quantitative measurements of CBF in acute ischemic stroke patients using pCASL perfusion imaging. The tissue-level CBF changes were evaluated and their correlations with patient clinical outcome were explored. Our results showed different CBF values between hypoperfused tissues recruited into infarction and those that survived. Moreover, a significant correlation was found specifically between the CBF reduction in benign oligemia area and patient neurological deficit severity. The CBF value derived by ASL without using exogenous contrast provides useful insights in early diagnosis of acute stroke patients.

II. METHODS

A. Patients

Eighteen acute ischemic stroke patients with a mean age of 67 years (range 40 to 84 years) within 24 h of symptom onset were prospectively recruited in our study. Demographics of the patients are listed in Table I. Two patients received thrombolytic therapy. Exclusion criteria included the presence of a contraindication for MRI, hemorrhage, or a non-stroke lesion on structural MRI. The neurological function was measured by the National Institute for Health Stroke Scale (NIHSS) score at admission. The mean NIHSS score of the patients was 6 (range 1 to 12). Based on the NIHSS score, the patients could be divided into two groups [14], i.e., mild stroke

This research was supported by National Natural Science Foundation of China (No. 81871083) and Shanghai Jiao Tong University Scientific and Technological Innovation Funds (2019QYA12).

Zengping Lin and Yao Li (Tel: +86-21-62932981; e-mail: yaoli@sjtu.edu.cn) are with School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, 200030, P.R. China. Tianyao Wang is with the Fifth People's Hospital of Shanghai, Fudan University, Shanghai 200240, P. R. China.

(≤ 5) and moderate stroke (6 – 12). Each group had nine patients. This study was approved by the Institutional Review Board of the Fifth People's Hospital of Shanghai, China. Written informed consents were obtained from all participants.

TABLE I. DEMOGRAPHICS OF THE PATIENTS

Patient	Syndrome	Sex	Age	NIH SS	Onset time (hr)	Follow-up (d)
1	PACS	M	59	7	6	34
2	PACS	M	40	4	24	96
3	TACS	M	49	7	14	30
4	PACS	M	63	12	3	12
5	PACS	M	78	4	13	8
6	LACS	F	82	1	15	29
7	LACS	M	69	3	15	8
8	LACS	M	67	4	6	10
9	PACS	F	77	2	12	7
10	PACS	M	77	7	24	9
11	PACS	F	84	5	24	15
12	PACS	M	62	12	12	9
13	POCS	M	68	9	8	7
14	PACS	F	78	7	22	10
15	PACS	M	81	10	2	9
16	PACS	M	64	9	24	12
17	PACS	M	51	4	12	7
18	PACS	M	55	2	24	8

NIHSS = National Institute for Health Stroke Scale; LACS = lacunar stroke; TACS = total anterior circulation stroke; PACS = partial anterior circulation stroke; POCS = posterior circulation stroke.

B. Image Acquisition

All the MR scans were performed on a 3.0T Siemens Skyra scanner. The first scan was performed within 24 h of patient symptom onset to acquire the structural and perfusion images. The follow-up scan was performed at 7-96 days post stroke to determine the final infarct. The image acquisition protocol for initial structural MRI scans included 3D magnetization prepared rapid gradient echo imaging (MPRAGE) imaging (repetition time (TR) / echo time (TE) / inversion time (TI) = 2400/2.13/1100 ms, resolution = 1.0 × 1.0 × 1.0 mm^3, field of view (FOV) = 256 mm, 192 slices), diffusion-weighted imaging (DWI) (TR/TE = 8300/74 ms, resolution = 2 × 2 × 2 mm^3, FOV = 256 mm, 75 slices, b = 1000 s/mm^2). For the follow-up scan, a 3D Fluid-Attenuated Inversion Recovery (FLAIR) imaging (TR/TE/TI = 5000/395/1800 ms, resolution = 1.0 × 1.0 × 1.0 mm^3, FOV = 256 mm, 192 slices) was performed.

C. Perfusion-Weighted Magnetic Resonance Imaging

The pCASL sequence with multiple post labeling delays was used in the initial MR scan to for perfusion imaging. The imaging parameters were as follows: resolution = 3.75 × 3.75 × 3.75 mm^3, FOV = 240 mm, TR = 3.2s, 3.4s 3.9s, 4.6s, 5.4s, TE = 10.3 ms, TI = 150 ms, 34 slices, labeling duration = 1.5s, post labeling delays = 0.8 s, 1.0 s, 1.5 s, 2.2 s, 3.0 s. The postprocessing of the ASL images was performed using the ASL toolbox [15] and Statistical Parametric Mapping 12 (SPM12). Briefly, the images were firstly realigned to the M_0 reference image for head motion correction, and then spatially smoothed by a 3D isotropic Gaussian kernel with full width half maximum (FWHM) of 5 mm. After that, a two-compartment perfusion model was utilized to generate the CBF images.

D. Regions of Interest Definition

The acute DWI lesion was defined by applying a threshold at 620×10^{-6} mm^2/s to the apparent diffusion coefficient (ADC) data [16]. The final infarct area was manually delineated on the follow-up FLAIR images. The perfusion deficit area was defined by a threshold of 20 ml/100g/min [16] on the CBF map within the gray matter mask, which was generated from the corresponding MPRAGE images using the unified segmentation routine in SPM12. Three regions of interest (ROIs) were defined for tissue-level analysis: a) infarct core: region in both the acute DWI lesion and final infarct area; b) infarct growth: region in the final infarct but not in the acute DWI lesion area; c) oligemia: region in the perfusion deficit area but not in the DWI lesion nor the final infarct area.

E. Image Registration

The ADC, DWI, FLAIR maps, and the corresponding tissue masks were all registered to the CBF images using an affine linear transformation with 12 degrees of freedom by FMRIB's Linear Image Registration Tool. All the masks were visually inspected by an experienced neuroradiologist and manually corrected where necessary.

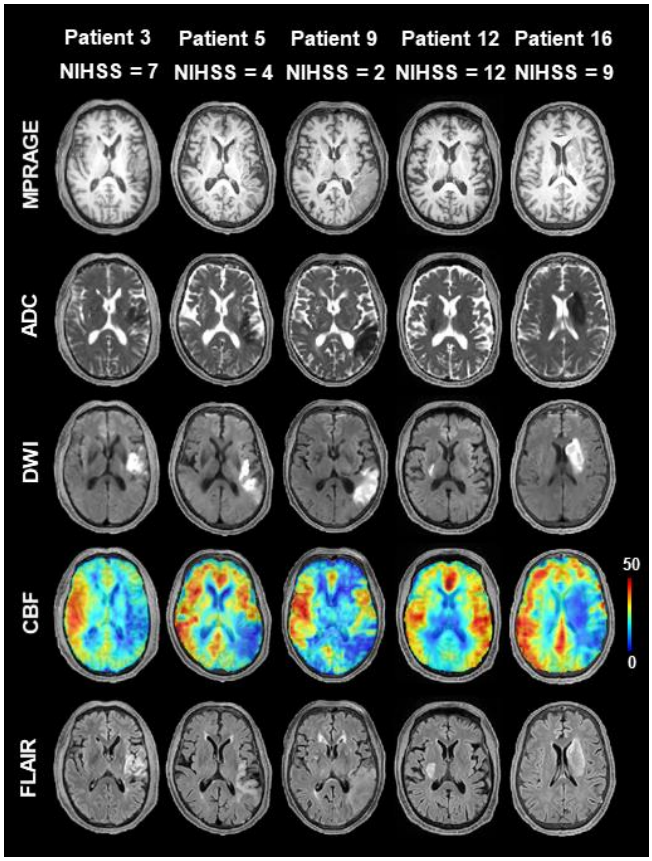

Figure 1. Multimodal images from representative patients. All the images were registered to the structural MPRAGE images. The ADC, DWI, and CBF images were acquired in the first scan. The FLAIR images were acquired in the follow-up session. The color bar for ASL-PWI images shows the CBF in ml/100g/min.

F. Statistical Analysis

The statistical analysis was performed using SPSS25 software (IBM). One-way ANOVA and paired t-test were used to compare the mean CBF values between different ROIs across patients. Independent t-tests were conducted to assess the differences in the mean CBF values between patients with mild stroke and moderate stroke. Pearson correlation analysis was performed to investigate the relationship between patients CBF value and NIHSS score.

III. Results

Multimodal images including MPRAGE, ADC, DWI, CBF, and follow-up FLAIR maps from five representative patients with NIHSS score ranging from 2 to 12 are shown in Fig. 1. We could visualize significant CBF signal reduction in the vicinity of the lesion area. Figure 2 illustrates the definition of the ROIs and the comparisons of mean CBF among the regions. One-way ANOVA showed a significant difference of the CBF values among different regions ($p < 0.0001$). As shown in Fig. 2(b), the CBF value of the infarct core was significantly lower than that of the infarct growth area ($p < 0.0001$), which in turn was lower than that of the oligemia region ($p < 0.01$). Figure 3 shows the comparison of mean CBF values between mild and moderate stroke groups for each ROI, respectively. The CBF of oligemia region in mild stroke group was significantly higher than that of moderate stroke group ($p < 0.05$). No between-group differences were found in the other two regions. Moreover, a significant negative correlation was found between the oligemia CBF and patient NIHSS score ($r = -0.48$, $p = 0.04$), as shown in Fig. 4. No correlation was found between the CBF value in infarct core or infarct growth area with patient NIHSS score.

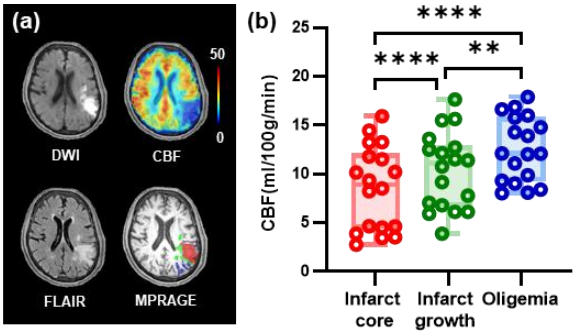

Figure 2. (a) Definition of regions of interest. Red: infarct core (region in both the acute DWI lesion and final infarct area), green: infarct growth (region in the final infarct but not in the acute DWI lesion area), and blue: oligemia (region in the perfusion deficit area but not in the DWI lesion nor the final infarct area). (b) Comparisons of mean CBF values among different regions within hypoperfused tissue.

IV. Conclusions and Discussions

In this study, we investigated the CBF reduction in different hypoperfused regions of acute ischemic stroke patients using pCASL perfusion imaging methodology. The differences in CBF value among infarct core, infarct growth and oligemia regions were observed. More interestingly, the mean CBF value in the oligemia area was significantly different in mild and moderate patients. Also, the oligemia CBF value was significantly correlated with patient NIHSS score, indicating the close relationship between patient perfusion deficit and the clinical outcome.

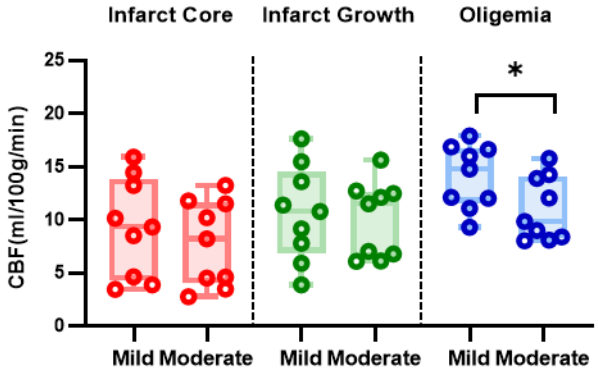

Figure 3. Comparisons of mean CBF values of infarct core, infarct growth, and oligemia area between mild and moderate stroke groups.

Our results showed that the quantitative CBF value measured by pCASL differed between benign oligemia and infarct growth area. The mean CBF value was 10.35 ml/100g/min for the infarct growth area and 12.56 ml/100g/min for the oligemia area, which corresponded well with the previous PET study. Using ^{15}O-PET, Furlan et al. found a CBF value of 11.4 ml/100g/min for penumbra progressed into infarction, while the CBF was at about 12.8 ml/100g/min for the non-infarcted area [2]. The mean CBF value in the core area in our study was 8.56 ml/100g/min, which was consistent with the threshold of CBF at 8 ml/100g/min recorded by hydrogen clearance for the neuronal membrane failure [17]. These results confirmed the validity of pCASL technology in providing accurate assessment of CBF in different hypoperfused tissues of acute ischemic stroke patients.

Utilizing pCASL imaging, we found the significant correlation between CBF reduction in the oligemia area and the neurological deficit severity of acute stroke patients. Warach et al. first reported that the perfusion information measured by DSC-MRI helped in the clinical assessment of acute stroke patients [4]. Tong et al. found an association between DSC-measured perfusion deficit size and NIHSS score in acute stroke patients [18]. Using continuous arterial spin labeling (CASL), the CBF of the affected hemisphere was found to be significantly correlated with NIHSS score of acute ischemic stroke patients [19]. In our study, we subdivided the perfusion deficit area into infarct core, infarct growth and oligemia area. We found, for the first time, that it was the mean CBF value within the benign oligemia region, but not the infarct core nor infarct growth area, that was correlated with patient NIHSS score. Our findings provide a tissue-specific CBF biomarker for the assessment of neurological deficit in acute stroke patients.

In summary, we applied pCASL to investigate the tissue-level CBF changes in the hypoperfusion region of acute ischemic stroke patients. The CBF reduction in the benign oligemia was predictive for the severity of patient neurologic deficit. Our work showed the great potentials of pCASL perfusion imaging in providing an effective assessment of tissue-level CBF information, which could be used as a valuable diagnostic tool in clinical acute stroke studies.

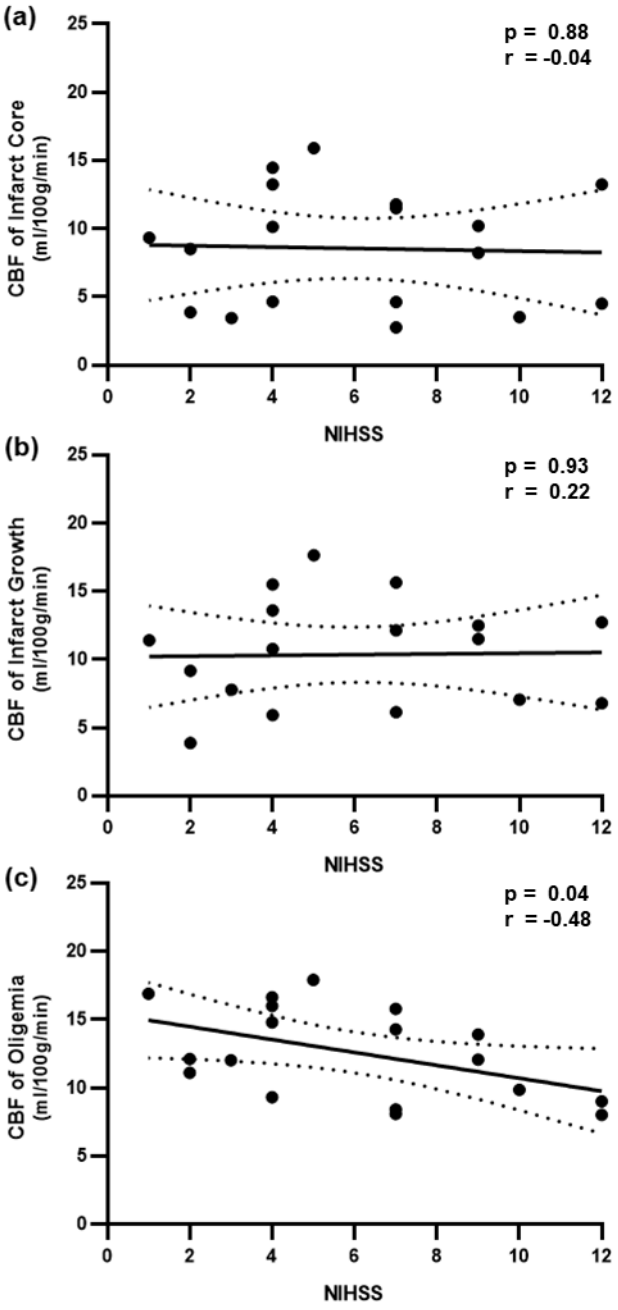

Figure 4. The scatter plots of CBF values in different hypoperfusion regions versus patients NIHSS score: (a) infarct core, (b) infarct growth, (c) oligemia. A significant negative correlation between NIHSS score and CBF values in the oligemia area was found, but not in infarct core and infarct growth area.

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