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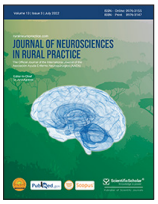

Original Article

Comparison of arterial spin labeling perfusion with dynamic susceptibility contrast perfusion in Moyamoya disease

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ABSTRACT

Objectives: Moyamoya disease (MMD) leads to frequent ischemic/hemorrhagic manifestations. Our aim was to compare findings of arterial spin labeling (ASL) with dynamic susceptibility contrast (DSC) perfusion in patients of MMD

Materials and Methods: Patients diagnosed as MMD underwent magnetic resonance imaging with ASL and DSC perfusion sequences. Perfusion in bilateral anterior cerebral artery and middle cerebral artery territories at two levels (level of thalami and centrum semiovale) was graded as normal (score 1), or reduced (score 2) on DSC and ASL cerebral blood flow (CBF) maps by comparison with normal cerebellar perfusion. Time to peak (TTP) maps of DSC perfusion were also qualitatively scored as normal (score 1), or increased (score 2) similarly. Correlation between scores of ASL, CBF, DSC, CBF, and DSC, TTP maps was assessed by using Spearman's rank correlation.

Results: Among the 34 patients, we did not find any significant correlation between the ASL CBF maps and DSC CBF maps ($r = -0.028$, $P = 0.878$), mean matching index 0.39 ± 0.31, whereas significant correlation was noted between the ASL CBF maps and DSC TTP maps ($r = 0.58$, $P = 0.0003$), mean matching index 0.79 ± 0.26. ASL CBF underestimated the perfusion compared to DSC perfusion.

Conclusion: ASL perfusion CBF maps do not match the DSC perfusion CBF maps and rather match the TTP maps of DSC perfusion. This is explained by inherent problems in estimation of CBF in these techniques because of delay in arrival of label (in ASL perfusion) or contrast bolus (in DSC perfusion) due to the presence of stenotic lesions.

Keywords: Arterial spin labeling, Cerebral blood flow, Cerebrovascular disorder, Neuroimaging, Moyamoya disease, Perfusion

INTRODUCTION

Moyamoya disease (MMD) is characterized by stenotic and occlusive changes involving the supraclinoid segment of internal carotid artery along with basal fine net-like vascular network, which are known as "Moyamoya" vessels.[1] Clinical manifestations of MMD involve ischemic manifestations such as transient ischemic attacks (TIA) or stroke with cerebral infarction, intracerebral hemorrhage, headache, seizures, involuntary movements, cognitive deficits and mental retardation, visual disturbance, and psychiatric manifestations. Treatment is done by surgical revascularization procedures which are divided as: Direct, indirect, and combined bypass.[2]

Perfusion studies are important to evaluate hemodynamic information necessary for further management. Various methods of assessing perfusion on magnetic resonance imaging (MRI) are available, including contrast agent based methods (dynamic susceptibility contrast - [DSC] perfusion/T2* perfusion) and non-contrast perfusion methods (arterial spin labeling - [ASL] perfusion). DSC perfusion utilizes the drop of T2/T2* signal intensity of brain parenchyma occurring during the passage of gadolinium contrast through the tissue capillary bed during first pass. It detects perfusion changes even in morphologically normal brain in patients with MMD.[3] It provides multiple useful parameters such as the "time of the maximum observed concentration (Tmax)," "Time to Peak (TTP)," and "Mean Transit Time (MTT)," which are important hemodynamic markers in MMD and are also helpful in determining success of revascularization surgery. Arterial spin-labeling (ASL) perfusion uses the labeled protons (endogenous tracer) in arterial blood which are labeled using radiofrequency pulses. For calculating

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cerebral blood flow (CBF), the amount of labeled blood reaching the parenchyma after a fixed time (after labeling) is measured by subtracting it from a control image obtained without labeled blood. As injection of contrast agent is not required in this modality, it is very advantageous for patients with kidney disease and also for imaging in Children.[4]

This study was carried out to evaluate the utility of ASL perfusion imaging in patients with MMD and to compare ASL perfusion with DSC perfusion in providing relevant hemodynamic information necessary for management.

MATERIALS AND METHODS

This was a prospective observational study. Ethics approval letter number: nimh/do/ethics sub-committee (BS & NS) 7th meeting/2017, date 22.11.2017, place: Nimhans, Bangalore. Inclusion criteria patient's demographic, clinical information and biochemical investigation reports were collected from the patient's outpatient/inpatient file and e-hospital portal of the institute. Information about symptoms and their duration and other demographic profile was taken in a predesigned pro forma.

Confirmation of diagnosis of MMD was based on magnetic resonance angiography/cerebral angiography diagnostic criteria (based on Guidelines for Diagnosis and Treatment of MMD).

Cooperative patients were taken up for MRI examination without sedation. For children <10 years, imaging/DSA procedure was done under anesthesia.

MRI were performed on 1.5T Aera (Siemens) and 1.5T Optima MR 450 w (GE) system. The pulse sequences and their parameters are mentioned in [Table 1].

Analysis of ASL and DSC perfusion

Cerebral perfusion was assessed in bilateral anterior cerebral artery (ACA) and middle cerebral artery (MCA) territories at two different levels (one at the level of the thalami, and another at level of the centrum semiovale, same level as Alberta Stroke Programme Early Computed Tomography Score locations).

Brain perfusion in bilateral ACA and MCA territories at both the levels was qualitatively graded as normal (score 1), or reduced (score 2) by comparison with normal cerebellar perfusion.

The imaging analysis was performed on IntelliSpace Portal 9.0 workstation (by Philips Healthcare). The subtracted ASL images were overlaid on the 3D T1 images and colored relative ASL perfusion maps were generated after motion correction. The fusion images were evaluated. Corresponding DSC perfusion images were similarly analyzed using IntelliSpace Portal 9.0 workstation (Philips Healthcare) and gamma variate processing was used to generate perfusion maps. CBF maps of ASL perfusion and DSC perfusion were analyzed for qualitative perfusion changes. TTP maps of DSC perfusion were also analyzed and qualitatively scored as normal (score 1), or increased (score 2) by comparison with normal cerebellar TTP. TTP maps were chosen because of the advantages of TTP in case of ischemia, that is, lesions in TTP maps are easily conspicuous and usually well-defined. In addition, TTP is a reproducible technique, as measurements obtained by different centers from a single data set are similar, with less technique-dependent artifacts to complicate interpretation.[5]

Data were expressed using descriptive statistics such as mean ± standard deviation for continuous variables and frequency percentages for categorical variables. Correlation between ASL CBF and DSC CBF was assessed using Spearman's rank correlation for the qualitative perfusion scores.

RESULTS

There were 34 patients, including 21 females and 13 male patients, with female to male ratio being 1.61. The mean age was 16.3 years, with age range from 2 to 58 years. There were 22 children (<18 years) and 12 adults (≥18 years). Thirty two patients (94.1%) had ischemic type of MMD, and 2 patients (5.9%) had hemorrhagic type. All children had ischemic type of MMD and 83.3% adults (10/12) had ischemic type and 16.7% of adult patients (2/12) had hemorrhagic type MMD.

Patients with ischemic type of Moyamoya disease (n = 32) presented with complaints of headache (n = 10, 31.5%), weakness (n = 27, 84.3%), seizures (n = 11, 34.3%), cognitive decline (n = 3, 9.3%), and personality change and psychosis (n = 1, 3.1%), in varying combinations.

Two patients who had hemorrhagic type of MMD presented with sudden onset of headache, vomiting, and loss of consciousness. Among patients presenting with weakness (n = 27), 20 patients had stroke and seven patients had TIA. MRI findings included cortical infarcts in n = 10 patients (29.4%), cortical watershed infarcts in n = 17 patients (50%), deep watershed infarcts in n = 15 patients (44.1%), and deep lacunar infarcts in n = 1 patient (2.9%). No infarct was seen in n = 6 (17.6%) patients. Two patients with hemorrhagic presentation had basal ganglia bleed with intraventricular hemorrhage. Demographic details, symptoms and MRI findings are tabulated in [Table 2].

On qualitative analysis of perfusion maps of ASL and DSC perfusion the matching index between DSC CBF maps and ASL CBF maps showed poor correlation (mean matching index 0.39 ± 0.31). On Spearman correlation analysis, we did not find any significant correlation between the CBF perfusion maps of ASL perfusion and CBF maps of DSC perfusion (r = −0.028, P = 0.878), as shown in [Table 3]. ASL CBF underestimated the perfusion compared to DSC perfusion.

Table 1: Pulse sequences and their parameters.

1.5 T Aera (Siemens)		**1.5 T Optima MR450w (GE)**	
T1-W Axial	TR/TE: 500 ms/11 ms; Slice thickness: 5 mm, 2D	T1-W Axial:	TR/TE: 2004.24 ms/8.76 ms; Slice thickness: 5 mm, 2D
T2 Axial, Coronal, Sagittal	TR/TE: 4500 ms/96 ms; Slice thickness: 5 mm, 2D	T2 Axial, Coronal, Sagittal	TR/TE: 5938.45 ms/110.7 ms; Slice thickness: 5 mm, 2D
FLAIR Axial	TR/TE: 9000 ms/88 ms; Slice thickness: 5 mm, 2D	FLAIR Axial	TR/TE: 12000 ms/98.7 ms; Slice thickness: 5 mm, 2D
DWI Axial	TR/TE: 3600 ms/83 ms; Slice thickness: 5 mm, 2D	DWI Axial	TR/TE: 8000 ms/101.6 ms; Slice thickness: 5 mm, 2D
SWI Axial	TR/TE: 49 ms/30 ms; Slice thickness: 2 mm, 2D	SWI Axial	TR/TE: 78.2 ms/48.8 ms; Slice thickness: 10 mm, 2D
TOF-MRA - multislab 3D	TR/TE: 32 ms/7 ms; Flip angle 25°, FOV read 200 mm Slice thickness: 0.7 mm, Voxel size : 0.4×0.4×0.7 mm,	TOF-MRA - multislab 3D	TR/TE : 22 ms/2.6 ms; Slice thickness: 1.4 mm
T1 MPRAGE 3D	TR/TE: 1800 ms/2.6 ms; Slice thickness: 1 mm, 3D	T1 BRAVO 3D	TR/TE: 9.5 ms/3.7 ms; Slice thickness: 1 mm, 3D
DSC perfusion	T2* perfusion, TR/TE: 1610 ms/30 ms, 20 slices, 50 measurements, Flip angle 90°, Voxel size: 1.8×1.8×5 mm, FOV read 230 mm, Slice thickness: 5 mm, EPI factor 128	DSC perfusion	T2* perfusion, TR 2000 ms, 20 slices, Flip angle 60°, FOV read 220 mm, Slice thickness: 5 mm
ASL perfusion	Pulsed 3D ASL, TR/TE: 4000 ms/16.38 ms, Flip angle 180°, FAIR QII mode, Inversion time 1800 ms, Voxel size: 3×3×3 mm, FOV read 192 mm, Slice thickness: 3 mm, Turbo factor 18, EPI factor 21	ASL perfusion	Pulsed continuous 3D ASL, TR/TE: 4766 ms/10.7 ms, Flip angle 180°, Inversion time 2025 ms, Voxel size: 3×3×3 mm, FOV freq 240 mm, Section thickness: 3 mm, Number of sections 40, matrix 512×8, Labelling time 1.5 s, Post label delay 1525
Post contrast T1 MPRAGE 3D	TR/TE: 1800 ms/2.6 ms; Slice thickness: 1 mm, 3D	Post contrast T1 BRAVO 3D	TR/TE: 9.5 ms/3.7 ms; Slice thickness: 1 mm, 3D

ASL: Arterial Spin Labeling, DSC: Dynamic Susceptibility Contrast, TOF-MRA: Time-of-flight magnetic resonance angiography, DWI: Diffusion-weighted imaging, SWI: Susceptibility weighted imaging, GE: GE Healthcare, FOV: Field of View, TR/TE: Repetition Time/ Echo Time, EPI: Echo Planar Imaging

However, there was significant correlation between CBF maps of ASL perfusion and TTP maps of DSC perfusion (mean matching index 0.79 ± 0.26). On Spearman correlation analysis, we found significant correlation between the CBF perfusion maps of ASL perfusion and TTP maps of DSC perfusion (r = 0.58, *P* = 0.0003), as shown in [Table 4]. Examples of qualitative analysis of perfusion maps are shown in [Figure 1].

DISCUSSION

We observed that perfusion maps of ASL perfusion were qualitatively similar to TTP maps of DSC perfusion. Wolf *et al.* reported similar results using ASL and demonstrated that TTP maps of DSC perfusion correlated best with ASL perfusion MR CBF values (both subjectively as well as objectively) when all patients in the study were considered. However, when cases with a major transit delay were excluded, then DSC relative CBF (rCBF) values correlated best with ASL CBF values.[6]

On qualitative analysis of perfusion maps in our study, there was poor correlation between DSC CBF maps and ASL CBF maps, when we qualitatively graded perfusion as normal (score 1) and reduced (score 2). In a study by Goetti *et al*., they compared qualitative perfusion scores between ASL perfusion and DSC perfusion and showed a strong and significant correlation between the two. In addition, ASL perfusion had an accuracy, sensitivity and specificity of 93%, 94%, and 93%, respectively, for detecting decreased perfusion per territory while considering DSC as standard of reference. They used qualitatively graded perfusion in each territory as normal (score 1), reduced (score 2), or severely reduced (score 3). However, the results of our study were different from this study and qualitatively there was a lot of difference in perfusion maps of ASL perfusion and DSC perfusion. Our results are similar to study by Mutke *et al.* who found a weak correlation for DSC-relCBF versus ASL-relCBF (r = 0.24) and found a large spread of values in the Bland-Altman-plot attributed to unreliable CBF-measurement.[7]

A delay in arrival times of the labeled arterial water protons or the gadolinium bolus, as noted in cerebrovascular diseases and also in MMD, affects the CBF estimation in both the

Table 2: Demographic details, symptoms, and MRI findings.

S. No.	Age	Sex	Ischemic/ hemorrhagic	Symptoms	Stroke/TIA symptom	Infarct in MRI
1.	10	F	Ischemic	Right weakness, seizures, headache	Stroke	Left MCA cortical
2.	24	M	Ischemic	Psychosis, personality change		Right frontal watershed cortical watershed
3.	11	M	Ischemic	Left weakness, focal seizures	Stroke	Left centrum semiovale infarct deep watershed
4.	2	F	Ischemic	Seizures, B/L limb weakness	Stroke	Infarcts B/L watershed cortical and deep watershed
5.	32	F	Ischemic	Headache, anxiety depression		Left frontal watershed cortical watershed
6.	6	M	Ischemic	Right weakness	TIA	No infarct
7.	6	M	Ischemic	Left weakness, headache	TIA	No infarct
8.	24	F	Ischemic	Headache, cognitive dysfunction, Right weakness	Stroke	Infarct B/L watershed cortical and deep watershed
9.	4	M	Ischemic	Left weakness	Stroke	Right MCA cortical and deep lacunar
10.	14	F	Ischemic	Headache, B/L weakness, seizures	TIA	Right frontal watershed cortical watershed
11.	21	F	Hemorrhagic	Headache, vomiting, Loss of consciousness	Hemorrhagic	Right Basal Ganglia bleed with IVH
12.	11	F	Ischemic	Right weakness	Stroke	Left MCA cortical
13.	9	F	Ischemic	Right weakness	Stroke	Left centrum semiovale infarct deep watershed
14.	17	F	Ischemic	Left weakness, headache	TIA	Right PCA, posterior MCA infarct cortical and cortical watershed and deep watershed
15.	14	F	Ischemic	Left weakness	Stroke	Infarct B/L watershed cortical, cortical watershed and deep watershed
16.	5	F	Ischemic	Right weakness	Stroke	Left frontal corona deep watershed
17.	22	F	Hemorrhagic	Right weakness, headache, vomiting	Hemorrhagic	Left BG bleed with IVH with chronic Left MCA-PCA infarct
18.	11	M	Ischemic	Left weakness	TIA	Deep watershed
19.	25	F	Ischemic	Seizures, cognitive decline		No infarct
20.	58	F	Ischemic	Left weakness, seizures	Stroke	Right watershed ACA cortical, cortical watershed and deep lacunar
21.	13	M	Ischemic	Right weakness	TIA	No infarct
22.	33	M	Ischemic	Left weakness	Stroke	Right ACA, watershed infarct cortical, cortical watershed and deep watershed
23.	27	F	Ischemic	Right weakness, headache	Stroke	Left MCA cortical
24.	15	M	Ischemic	Right weakness	Stroke	Left CS infarct deep watershed
25.	9	M	Ischemic	Left weakness	TIA	No infarct
26.	21	M	Ischemic	Right weakness	Stroke	Left MCA-PCA corttical watershed and deep watershed
27.	4	F	Ischemic	Right focal seizure		No infarct
28.	12	F	Ischemic	Right focal seizure, Right weakness, cognitive decline	Stroke	Left frontal, parieto-occipital watershed cortical watershed and deep watershed
29.	19	M	Ischemic	Left weakness, headache	Stroke	B/L watershed cortical, cortical watershed and deep watershed
30.	18	F	Ischemic	Right weakness	Stroke	Left MCA, watershed cortical and cortical and deep watershed
31.	17	F	Ischemic	Headache		B/L watershed deep watershed
32.	15	M	Ischemic	Heaadache, seizure, Right weakness	Stroke	Left MCA-PCA watershed cortical watershed
33.	12	F	Ischemic	Seizure, Left weakness	Stroke	B/L watershed cortical watershed and deep watershed
34.	15	F	Ischemic	Right weakness, giddiness	Stroke	Left MCA-PCA watershed cortical watershed

TIA: Transient ischemic attacks, MCA: Middle Cerebral Artery, ACA: Anterior Cerebral Artery, PCA: Posterior cerebral artery, MRI: Magnetic resonance imaging, IVH: Intraventricular hemorrhage

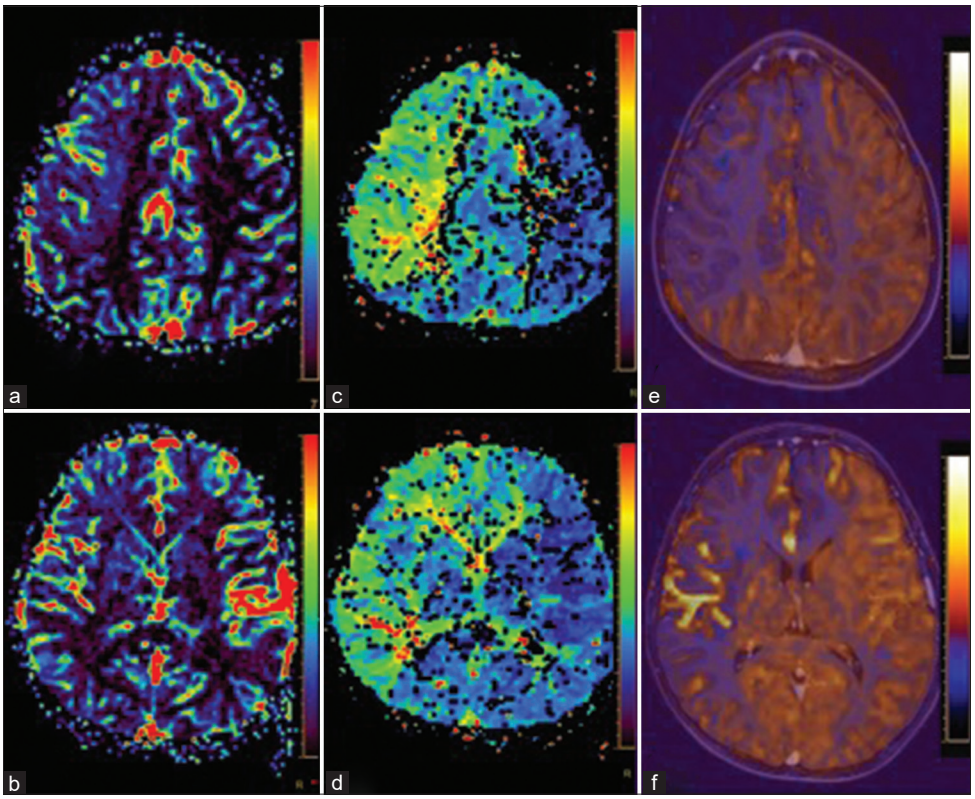

Figure 1: A 6-year-old child presented with history of episodes of the left-sided weakness for 1 month, headache for 15 days. DSC perfusion CBF maps (a and b) do not show any perfusion abnormality. DSC perfusion TTP maps (c and d) show increased TTP in the right cerebral hemispheres in right ACA, MCA territories and in the left ACA territory. ASL-CBF maps (e and f) show reduced perfusion in right ACA, MCA territories and in the left ACA territory. Areas of ASL-CBF map abnormalities are matching with areas of DSC-TTP map abnormalities on visual qualitative analysis. This was seen in most patients and was statistically significant. DSC: Dynamic susceptibility contrast, CBF: Cerebral blood flow, TTP: Time to peak, ACA: Anterior cerebral artery, MCA: Middle cerebral artery, ASL: Arterial spin labeling.

Table 3: Results of correlation of qualitative perfusion scores between CBF maps of ASL perfusion and CBF maps of DSC perfusion using Spearman correlation analysis.

	ASL_ RIGHT_CBF	ASL_ LEFT_CBF	ASL_ CBF
SPEARMAN'S RHO			
DSC_RIGHT_CBF			
Correlation coefficient	−0.042	−0.200	−0.158
Sig. (2-tailed)	0.819	0.265	0.379
n	33	33	33
DSC_LEFT_CBF			
Correlation coefficient	0.078	0.048	0.067
Sig. (2-tailed)	0.665	0.791	0.713
n	33	33	33
DSC_CBF			
Correlation coefficient	0.032	−0.062	−0.028
Sig. (2-tailed)	0.859	0.732	0.878
n	33	33	33

CBF: Cerebral blood flow, ASL: Arterial spin labeling, DSC: Dynamic susceptibility contrast. None of the values are significant.

Table 4: Results of correlation of qualitative assessment of CBF maps of ASL perfusion and TTP maps of DSC perfusion using Spearman correlation analysis.

	DSC_RIGHT_ TTP	DSC_ LEFT_TTP	DSC_ TTP
SPEARMAN'S RHO			
ASL_RIGHT_CBF			
Correlation coefficient	0.525**	0.312	0.428**
Sig. (2-tailed)	0.002	0.077	0.013
n	33	33	33
ASL_LEFT_CBF			
Correlation coefficient	0.066	0.809**	0.580**
Sig. (2-tailed)	0.713	0.000	0.000
n	33	33	33
ASL_CBF			
Correlation coefficient	0.315	0.667**	0.589**
Sig. (2-tailed)	0.074	0.000	0.000
n	33	33	33

ASL: Arterial spin labeling, CBF: Cerebral blood flow, DSC: Dynamic susceptibility contrast, TTP: Time to peak. None of the values are significant.

modalities. For DSC perfusion, this bolus arrival delay causes bolus dispersion and thus leads to underestimation of rCBF and the overestimation of MTT.[8] For ASL perfusion, delayed transit times do not allow blood to reach tissue parenchyma at the time of image acquisition leading to loss of perfusion signal and artificially low CBF values.[9] On the other hand, at the time of acquisition, the labeled blood may be present in the collaterals leading to false high intra-arterial signal (Arterial Transit Artifact) which can be misinterpreted as hyperperfusion. These inherent problems in DSC and ASL perfusion methods are responsible for the complex interpretation of their maps and thus leading to various incongruence in various studies, all of which use different method of acquisition, post processing methods, labeling duration, post label delay, etc.

To overcome the deleterious effect of delayed transit time on estimation of CBF in ASL perfusion, nowadays use of multiphase ASL is being promoted. Recently, Yun *et al*. evaluated the usefulness of transit time corrected CBF maps using multiphase ASL-MR perfusion imaging and they concluded that the use of transit time corrected CBF maps can overcome the effect of delayed transit time on conventional ASL perfusion maps.[10] In a study by Fan *et al*., they noted that standard-delay conventional ASL underestimated rCBF. Transit times correction using multidelay ASL acquisitions led to improved correlation with positron emission tomography (PET), while still underestimating CBF in the cases with long transit delays. However long-label long-delay ASL scans had the strongest correlation with PET. They concluded that post-label delay times of ≥4 s are required in correct estimation of CBF in MMD using ASL perfusion, and this may be combined with using multidelay strategies for accurate ASL assessment of CBF in these patients.[11]

Our results show that on qualitative visual analysis, ASL perfusion CBF maps do not match the DSC perfusion CBF maps and rather match the TTP maps of DSC perfusion. This is explained by inherent problems in estimation of CBF in these techniques because of delay in arrival of label (in ASL perfusion) or contrast bolus (in DSC perfusion) due to the presence of stenotic lesions.

Our study has few limitations. The studies were performed in two machines using pulsed ASL and pseudocontinuous ASL techniques. Children <10 years (n = 8) underwent MRI under sedation and effect of anesthetic medication might have altered the measured CBF. Mutidelay ASL sequence was not available which is more accurate for the estimation of CBF as transit-time corrected CBF maps are provided using this method. Perfusion parameters using Gold standard perfusion estimation methods such as Single Photon Emission Computed Tomography/O−15 PET were not evaluated.

CONCLUSION

ASL CBF maps correlate well with TTP maps of DSC perfusion and do not correlate with CBF maps of DSC perfusion. The information regarding perfusion given by these two modalities (ASL perfusion and DSC perfusion) is different and should be interpreted keeping these incongruences in mind. Multi-delay ASL and long delay ASL may be required for better estimation of CBF in patients of MMD.

Declaration of patient consent

Ethical committee approval was obtained.

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Nil.

Conflict of interest

There is no conflict of interest.

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