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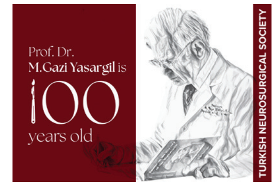

Comparison of Pre-Operative and Post-Operative Mean Transit Time Delay in Ipsilateral and Contralateral Hemispheres in Moyamoya Disease Using DSC Perfusion

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ABSTRACT

AIM: To perform comparison of preoperative and postoperative mean transit time (MTT) delay in ipsilateral, and contralateral hemispheres in Moyamoya disease using dynamic susceptibility contrast (DSC) perfusion.

MATERIAL and METHODS: Preoperative images were obtained within 1 week before surgery and postoperative images were taken 3 months after surgery. Cerebral perfusion was assessed in bilateral middle cerebral artery territories with 3 Region Of Interest (ROI) on each side (ipsilateral and contralateral to surgery side). Two ROI were also drawn in bilateral cerebellar hemisphere. MTT delay at each middle cerebral artery (MCA) region was calculated by subtracting MCA territory ROI MTT value from ipsilateral cerebellar ROI MTT value. Non-normally distributed measurement data are expressed as the median [interquartile range (IQR)] and compared using Wilcoxon's rank-sum test. $p<0.05$ was considered statistically significant.

RESULTS: Median ipsilateral MTT delay values (in seconds) before surgery were 2.4, Interquartile Range (IQR) 4.95; and after surgery was 1, IQR 2.1 We noted a significant decrease in postoperative MTT delay values on ipsilateral side compared with preoperative values ($p=0.008$). Contralateral MTT delay values did not show this trend. Median contralateral MTT delay values (in seconds) before surgery were 0.6, IQR 3.7; and after surgery was 1.6, IQR 3.65 We noted no significant difference in preoperative and postoperative MTT delay values on contralateral side ($p=0.12$).

CONCLUSION: DSC perfusion analysis of MTT delay in follow up imaging after revascularization surgery can be helpful in deciding success of surgery. Evaluation of contralateral hemisphere perfusion can be helpful to guide regarding need of contralateral side surgery. Future studies to evaluate contralateral perfusion characteristics are necessary to understand the complex hemodynamic changes which occur post revascularization surgery.

KEYWORDS: Moyamoya disease, Perfusion, MTT delay, Revascularization surgery, DSC perfusion

ABBREVIATIONS: MTT: Mean transit time, **DSC:** Dynamic susceptibility contrast, **ROI:** Region of interest, **MCA:** Middle cerebral artery, **IQR:** Interquartile range, **ICA:** Internal carotid artery, **MRI:** Magnetic resonance ımaging, **CBF:** Cerebral blood flow, **CBV:** Cerebral blood volume, **TTP:** Time to peak, **EDAMS:** Encephalo-duro-arterio-myo-synangiosis, **STA-MCA:** Superficial temporal artery- middle cerebral artery, **CT:** Computed tomography, **SPECT:** Single photon emission computed tomography, **O-15 PET:** Oxygen-15 photon emission tomography, **CVR:** Cerebrovascular reserve

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INTRODUCTION

Moyamoya disease (MMD) is a chronically progressive cerebrovascular disease that is associated with narrowing of supraclinoid internal carotid arteries (ICAs) along with basal fine net-like vascular network, which is known as "moyamoya" vessels (16). It presents with ischemic or hemorrhagic symptoms.

Surgical revascularization procedures aim to improve the state of the cerebral circulation to decrease the risk of future strokes and are categorized into direct, indirect, and combined bypass. Postoperative imaging usually includes magnetic resonance imaging (MRI) to evaluate the parenchyma and angiography to assess revascularization development. Postoperative revascularization is graded on angiography with the Matsushima and Inaba grading (14). However, it is invasive and does not provide hemodynamic and cross-sectional information. Thus, adding perfusion imaging is useful in the follow-up of patients after surgical revascularization. Mean transit time (MTT) is a crucial parameter to assess parenchymal perfusion because a delay in MTT helps diagnose ischemic areas. We conducted preoperative and postoperative perfusion analysis in seven patients with MMD to identify its use in postoperative imaging.

MATERIAL and METHODS

This was a prospective observational study. The study was done after ethical committee approval (letter number NIMH/DO/ETHICS SUB-COMMITTEE {BS & NS} 7TH MEETING/ 2017 dated 22/11/2017), and patient consent was taken. 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 proforma.

Confirmation of diagnosis of moyamoya disease was based on MR angiography/cerebral angiography diagnostic criteria (based on Guidelines for Diagnosis and Treatment of moyamoya disease). Cooperative patients were taken up for MRI examination without sedation, for children <10 years, imaging/DSA procedure was done under anaesthesia.

MRI was performed on 1.5T Aera (Siemens) or 1.5T Optima MR450w (GE) system.

Preoperative images were obtained within 1 week before surgery and postoperative images were taken 3 months after surgery. DSC perfusion images were analyzed quantitatively using IntelliSpace Portal 9.0 workstation (Philips Healthcare) and gamma variate processing was used to generate perfusion maps and maps of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to peak (TTP) were generated and values of these parameters were estimated.

Cerebral perfusion was assessed in bilateral middle cerebral artery territories with 3 ROI on each side (ipsilateral and contralateral to surgery side): MCA^1- ROI involving cortical MCA territory at level of centrum semiovale, MCA^2: ROI involving cortical MCA territory at level of thalamus and MCA^{bg}- ROI drawn at basal ganglia). These ROI were drawn in reference to previous studies (4,17). Two ROI were also drawn in bilateral cerebellar hemisphere at level of middle cerebellar peduncles for cerebellar perfusion assessment. ROI are shown in Figure 1. MTT delay at each MCA region was calculated by subtracting MCA territory ROI MTT value from ipsilateral cerebellar ROI MTT value. Non-normally distributed measurement data are expressed as the median (interquartile range [IQR]) and compared using Wilcoxon's rank-sum test. $p<0.05$ was considered statistically significant.

RESULTS

A total of 7 patients were recruited for the study. The demographic, clinical and preoperative morphologic MRI data of these patients are given in Table I. Details of management, follow up symptoms and follow up MRI is given in Table II. Three patients underwent Encephalo-duro-arterio-myo-synangiosis (EDAMS) and 4 patients underwent superficial temporal artery - middle cerebral artery (STA-MCA) bypass. STA-MCA bypass has been found to be superior to EDAMS for secondary stroke prevention and was preferred for the symptomatic hemisphere (8). However, if the caliber of the donor or the recipient vessel was not found suitable either during the preoperative evaluation or during surgery, then EDAMS was done.

We analysed the MTT delay values of hemispheres ipsilateral to operative side and contralateral to it.

Median ipsilateral MTT delay values (in seconds) before surgery were 2.4, Interquartile Range 4.95; and after surgery was 1, Interquartile Range 2.1 We noted a significant difference in preoperative and postoperative MTT delay values on ipsilateral side, with postoperative MTT showing a significant decrease in values compared to preoperative values (p=0.008).

Contralateral MTT values did not show this trend. Median contralateral MTT delay values (in seconds) before surgery were 0.6, Interquartile Range 3.7; and after surgery was 1.6, Interquartile Range 3.65 We noted no significant difference in preoperative and postoperative MTT delay values on contralateral side (p=0.12). Comparison of preoperative and postoperative ipsilateral and contralateral MTT delay values are shown in Figure 2, 3.

Postoperatively, all patients had ipsilateral benefit with no new symptoms and/or improvement in ipsilateral symptoms. 4 patients had contralateral symptoms in postoperative period. All four of these patients developed increase in MTT delay in one or more of MCA territories on perfusion imaging analysis, corresponding with their symptoms.

Examples of comparison of preoperative and postoperative MTT analysis are shown in Figure 4 and Figure 5.

DISCUSSION

Postoperative evaluation after revascularization surgery in MMD is usually performed by angiographic assessment with the Matsushima grading (14). However, it is invasive and does not provide hemodynamic information. Dynamic susceptibility

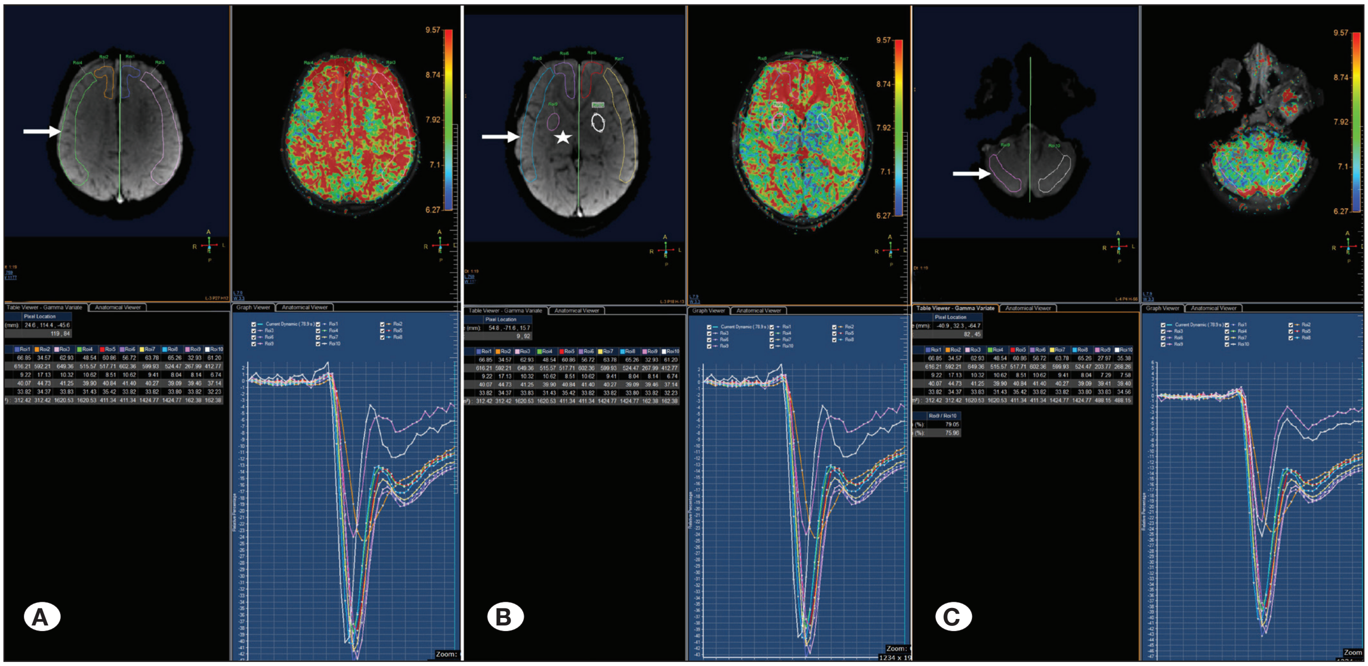

Figure 1: A) Arrow shows region of interest (ROI) drawn in cortical middle cerebral artery (MCA) territory (M^1) at level of centrum semivale. **B)** Arrow shows ROI drawn in cortical MCA territory (M^2) at level of thalamus. Marked Star (*) shows ROI drawn at basal ganglia (M^{bg}). **C)** Arrow shows ROI drawn involving cerebellar hemisphere.

Table I: Demographic, Clinical and Preoperative Morphologic MRI Data of Patients

No	Age (Years)	Sex	Ischemic/ Hemorrhagic	Symptoms	Stroke/ TIA Symptom	Infarct in MRI	IVY Sign
1	2	Female	Ischemic	Seizures, b/l limb weakness	Stroke	Infarcts bilateral (b/l) watershed cortical and deep watershed	No
2	24	Female	Ischemic	Headache, cognitive dysfunction, right weakness	Stroke	Infarcts b/l watershed cortical and deep watershed	No
3	4	Male	Ischemic	Left weakness	Stroke	Right mca cortical and deep lacunar	Yes
4	11	Female	Ischemic	Right weakness	Stroke	Left mca cortical infarct	Yes
5	14	Female	Ischemic	Left weakness	Stroke	Infarcts b/l watershed cortical, cortical watershed and deep watershed	Yes
6	9	Male	Ischemic	Left weakness	TIA	No infarct	Yes
7	6	Male	Ischemic	Right weakness	TIA	No infarct	Yes

***TIA:** Transient Ischemic Attack, **IVY Sign:** Refers to sulcal hyperintensities noted on Fluid Attenuated Inversion Recovery Sequence (FLAIR), denoting presence of collaterals in Moyamoya disease.*

contrast-enhanced (DSC) perfusion imaging on MRI is one of the important modalities used to evaluate hemodynamic changes.

We observed a significant difference in the preoperative and postoperative MTT values on the ipsilateral side, with the postoperative MTT demonstrating a significant decrease in values compared to the preoperative values (p=0.03). This is similar to the results of multiple studies exhibiting a decrease in MTT of the MCA territory on the ipsilateral side after unilateral surgical revascularization on computed tomography (CT) and MRI perfusion analysis (2,7,8,10-12,18-20) cerebral blood volume (CBV with MTT delay changes described as

Table II: Details of Management, Complications, Follow up Symptoms and Follow up MRI Findings

No	Surgery	Postoperative complication	Follow up symptoms	Follow up MRI	Contrlateral symptoms
1	EDAMS	None	Seizures frequency reduced	No fresh infarct	None
2	STA-MCA Bypass	None	Lower limb weakness persisting, upper limb weakness improved, no fresh symptoms	No fresh infarct	None
3	EDAMS	None	Weakness improved, no fresh ipsilateral symptoms	No fresh infarct	Yes
4	STA-MCA Bypass	None	Weakness improved, no fresh ipsilateral symptoms	No fresh infarct	Yes
5	EDAMS	None	Weakness improved, no fresh ipsilateral symptoms	No fresh infarct	None
6	STA-MCA Bypass	None	Weakness improved, no fresh ipsilateral symptoms	No fresh infarct	Yes
7	STA-MCA Bypass	None	Weakness improved, no fresh ipsilateral symptoms	No fresh infarct	Yes

EDAMS: *Encephalo-duro-arterio-myo-synangiosis,* ***STA:*** *Superficial temporal artery,* ***MCA:*** *Middle cerabral artery,* ***MRI:*** *Magnetic resonance imaging.*

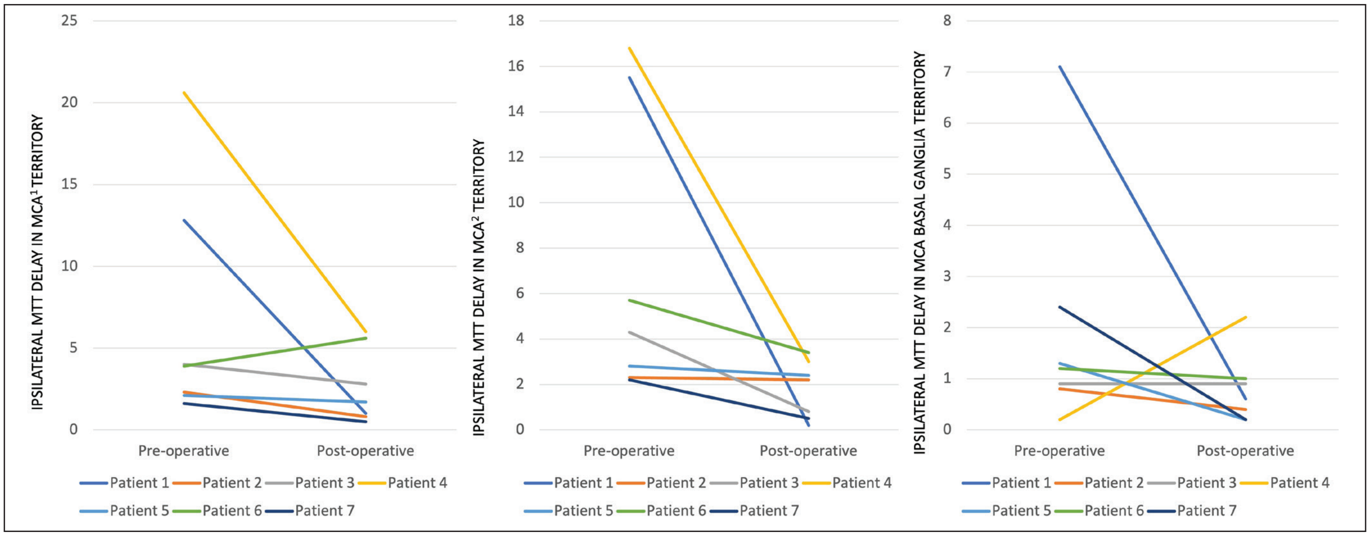

Figure 2: Graph showing preoperative vs postoperative mean transit time (MTT) delay changes in middle cerabral artery (MCA) territory in MCA^1, MCA^2 and MCA^{bg} territory in ipsilateral hemisphere with significant reduction in MTT delay (p=0.008).

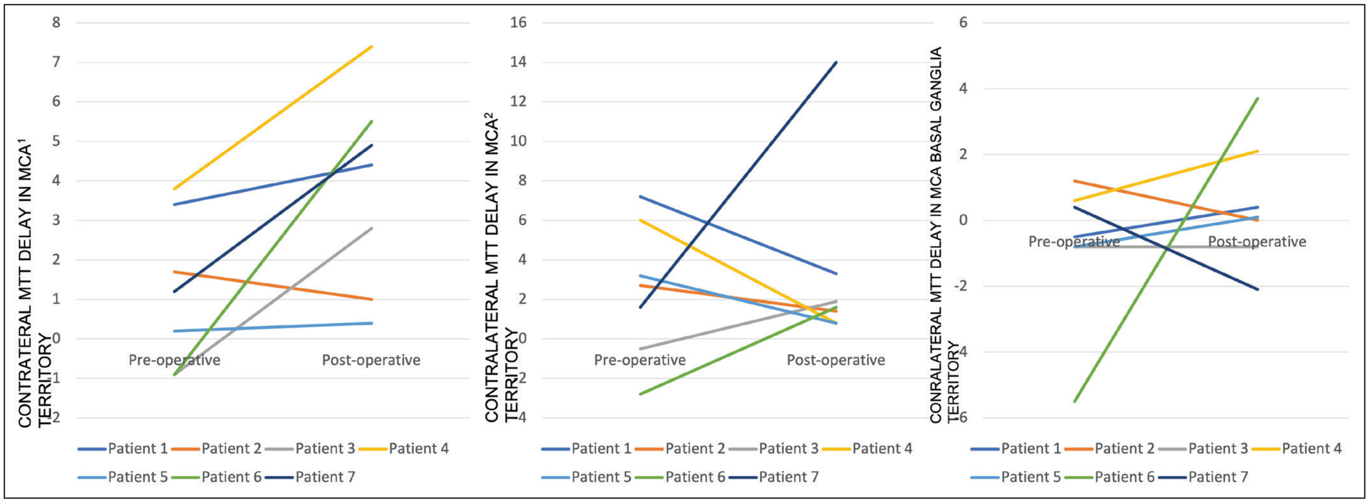

Figure 3: Graph showing preoperative vs postoperative mean transit time (MTT) delay changes in middle cerabral artery (MCA) territory in MCA^1, MCA^2 and MCA^{bg} territory in contralateral hemisphere with no significant changes in MTT delay (p=0.12).

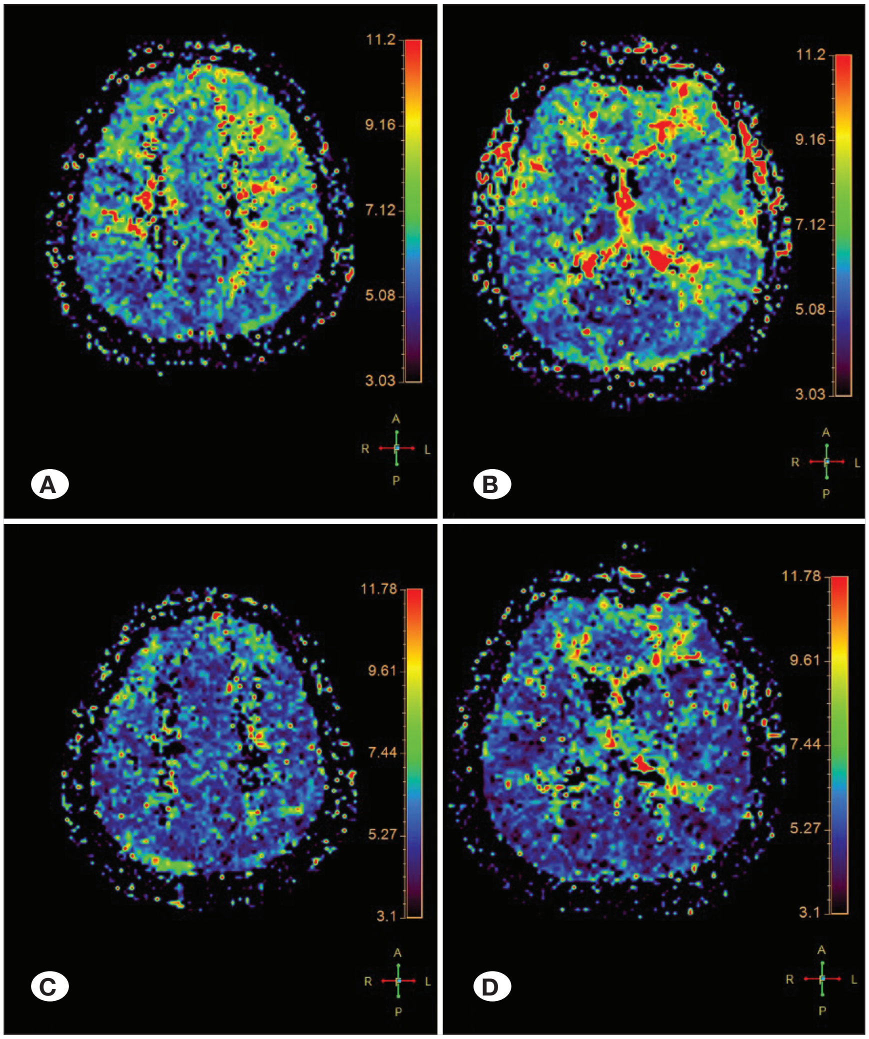

Figure 4: A 24-year-old female patient presented with history of headache and cognitive dysfunction for 2 years and recent onset of right sided weakness. Preoperative mean transit time (MTT) maps **(A,B)** showing raised MTT in bilateral hemispheres involving anterior circulation (left>right). Patient was operated on left side. Postoperative MTT maps **(C,D)** show decreased MTT following surgery on ipsilateral side (left hemisphere) as well as contralateral side (right hemisphere).

early as 2–4 weeks postoperatively (8). We revealed that MTT delay reduction correlated with symptom resolution in the postoperative period in all our patients.

In most centers, especially in developing countries, other postoperative imaging modalities, such as SPECT and O-15 PET, may not be readily available. Additionally, CT perfusion is not very readily available and most machines exhibit a limited coverage slab for CT perfusion, and whole brain perfusion analysis may not be readily available. Thus, follow-up MTT delay reduction on DSC perfusion imaging helps determine the success of surgery and should be routinely performed as a follow-up imaging.

All of the seven operated patients developed improvement in ipsilateral hemispheric symptoms postoperatively, whereas four patients developed contralateral hemispheric symptoms on follow-up. All four patients demonstrated an increase in MTT delay in one or more MCA territories. This observation is similar to a study by Ma et al. who revealed their experience in the perfusion evaluation of contralateral (nonoperated and asymptomatic) hemispheres in 15 MMD cases in whom unilateral direct bypass surgery of the symptomatic hemisphere was conducted. They demonstrated rCBF and cerebrovascular reserve (CVR) improvement on the ipsilateral side with decreased rCBF and CVR developing on the contralateral side on follow-up. The authors concluded that unilateral (symptomatic side) direct surgical revascularization for patients with MMD caused CVR impairment in the contralateral asymptomatic hemisphere (13). However, this study did not perform an angiographic follow-up of these patients who developed impaired CVR on the contralateral side, which could be caused by disease progression itself. We also did not conduct an angiographic follow-up of these patients who developed worsening of the contralateral MTT postoperatively on follow-up and developed symptoms on the contralateral side. Thus, disease progression may cause the development of contralateral perfusion worsening in these four patients.

In contrast, the recent literature shows a contralateral hemodynamic benefit (3). Bacigaluppi et al. revealed a contralateral hemodynamic improvement after unilateral direct bypass surgical revascularization, as demonstrated by improved CVR on postoperative quantitative MRI (1). Other perfusion studies in patients with MMD revealed a beneficial effect in the nontreat-

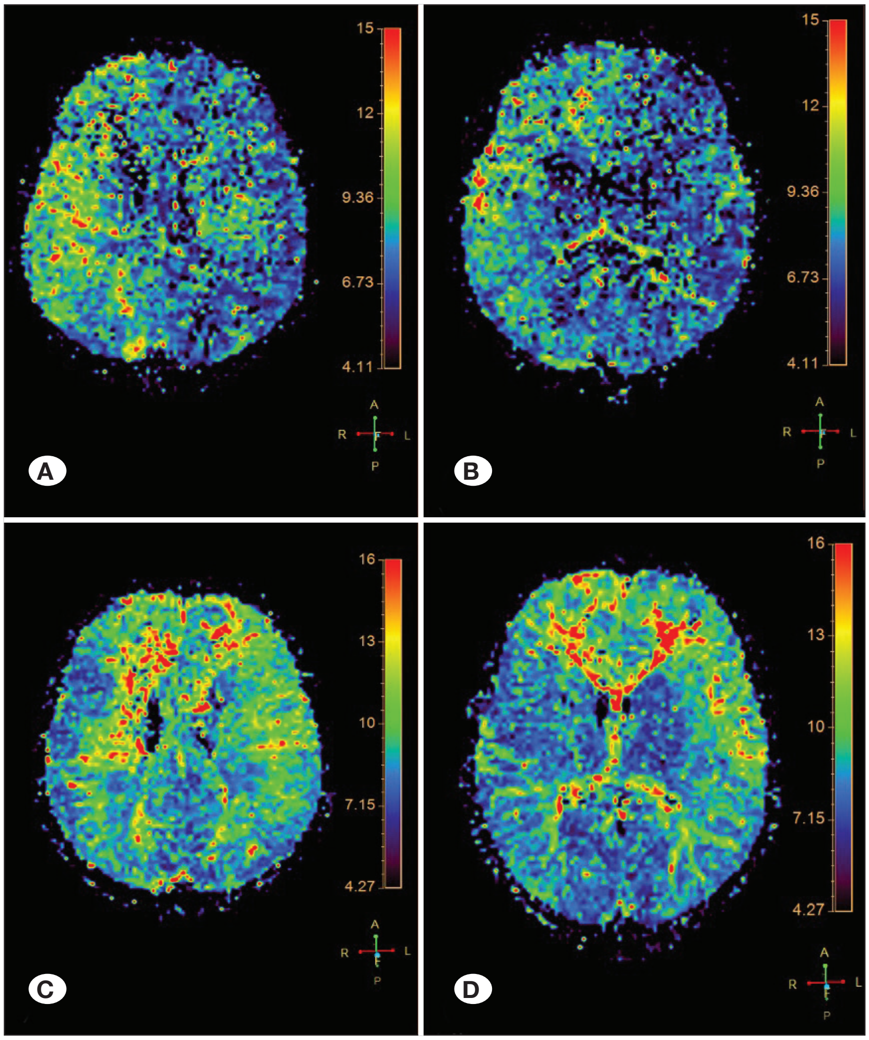

Figure 5: A 4-year-old male patient presented with a history of episodic left sided weakness for 4 months [recurrent transient ischemic attack (TIA)]. Preoperative mean transit time (MTT) maps **(A,B)** showing raised MTT in right cerebral hemispheres involving anterior circulation with mildly raised MTT in left cerebral hemisphere (anterior circulation). Patient was operated on right side. Postoperative MTT maps **(C,D)** show decreased MTT following surgery in MCA territory on ipsilateral side (right hemisphere) with marked increase in MTT on contralateral side (left hemisphere) postoperatively.

ed hemisphere after unilateral surgery (6,15). We exhibited that other patients who underwent surgery and did not develop contralateral symptoms and for whom DSC parameters were available for preoperative and postoperative comparison (n=3) demonstrated MTT improvement on the ipsilateral as well as the contralateral side. These incongruities are explained by the complex cerebral hemodynamic rearrangement that occurs postoperatively and the inherent underlying challenge in understanding these complex dynamic changes (3).

Huang et al. evaluated the hemodynamic difference between symptomatic and nonsymptomatic cerebral hemispheres in patients with symptomatic MMD using CT perfusion (5). They concluded that rCBF and rMTT were more sensitive than rTTP for assessing hemodynamic changes in patients with symptomatic bilateral MMS. Additionally, we observed that the increase in postoperative contralateral hemisphere MTT delay corresponded to the development of patient symptoms corresponding to the contralateral hemisphere. This observation emphasizes the importance of perfusion MRI, especially MTT analysis, which helps guide the decision for the side of surgery in case of bilateral symptoms.

CONCLUSION

DSC perfusion analysis of MTT delay in follow up imaging after revascularization surgery can be helpful in deciding success of surgery. Also evaluation of contralateral hemisphere perfusion can be helpful to guide regarding need of contralateral side surgery. Future studies to evaluate contralateral perfusion characteristics are necessary to understand the complex hemodynamic changes which occur post revascularization surgery.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: NY, HP
Data collection: NY, HP, AKG, CP, DS, SB
Analysis and interpretation of results: NY, HP, KT
Draft manuscript preparation: NY, HP
Critical revision of the article: NY, HP, AKG, CP, DS, SB
Other (study supervision, fundings, materials, etc...): NY, HP
All authors (NY, HP, AKG, CP, DS, KT, SB) reviewed the results and approved the final version of the manuscript.

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