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Original Article

Radiology Section

Whole Brain CT Perfusion Evaluation in Transient Ischaemic Attack: A Cross-sectional Study from a Tertiary Care Centre, New Delhi, India

PRATEEK KUMAR MADAAN[1], ROHINI GUPTA GHASI[2]

ABSTRACT

Introduction: Few studies exist in current literature regarding imaging features in Transient Ischaemic Attack (TIA) and most of the previous studies on Computed Tomography Perfusion (CTP) have used old generation scanners with limited brain coverage.

Aim: To study the spectrum of whole brain CTP parameters in patients presenting with TIA using a 256 slice CT scanner.

Materials and Methods: This cross-sectional observational study was conducted on 15 patients, tertiary care centre in New Delhi, India over a period of 18 months from October 2017 till March 2019. All patients presenting with the first episode of TIA were evaluated with Non Contrast Computed Tomography (NCCT), Whole brain CTP, and Colour doppler of carotid vessels. Quantitative assessment and statistical analysis of the alteration of CT perfusion parameters was done in areas of visualised Focal Perfusion Abnormalities (FPA) and seven predefined locations in bilateral hemispheres on perfusion maps.

Results: Five out of 15 patients had FPAs in the colour maps and there was a significant elevation of Cerebral Blood Flow (CBF) and Cerebral Blood Volume (CBV) in the FPA region (p-value=0.018) suggestive of postischaemic hyperperfusion. The mean hemispheric CBF was increased in the abnormal hemisphere compared to the normal hemisphere (p-value=0.04).

Conclusion: CTP parameters are significantly altered in the patients with TIA with predominant increase in CBF and CBV in the patients who have FPA on CTP. CTP shows postischaemic hyperperfusion changes in the form of increased CBF in the hemisphere corresponding to the symptoms.

Keywords: Cerebrovascular accident, Computed tomography perfusion, Postischaemic hyperperfusion, Stroke

INTRODUCTION

Transient Ischaemic Attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction [1]. Though distinct from stroke which has an essential component of infarction, studies have shown that 10-15% of TIA patients have a stroke within three months, with half occurring within 48 hours [1]. Thus, TIA can be considered as a sinister warning sign of impending stroke. Neuroimaging studies in patients with TIA are few and mostly focus on Diffusion and Perfusion Magnetic Resonance Imaging (MRI) [2-4]. CT Perfusion is acomparatively cheaper and faster modality and also more widely available throughout all tertiary care hospitals and even in some secondary care centres. It can play an important role, especially in a resource-constrained healthcare setting. A select few studies have been done so far on changes seen in TIA patients on Computed Tomography Perfusion (CTP) [5-8]. However, almost all these studies have been performed on old-generation CT scanners with limited brain coverage. Moreover, the normal limits of CT perfusion parameters have not been objectively defined yet and vary across studies and according to the model of CT scanner. The present study was performed to study the spectrum of whole brain CTP parameters in patients presenting with Transient Ischaemic Attack (TIA).

MATERIALS AND METHODS

A cross-sectional observational study was performed after due clearance from the Institutional Review Board (Ethics approval certificate number - IEC/VMMC/SJH/Thesis/October/2017-195) at a Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India, (tertiary care centre) for a period of 18 months from October 2017 to March 2019.

Inclusion criteria: All adult patients who presented with the first episode of TIA within the last 10 days were enrolled. Acute infarction was ruled out on Non Contrast Computed Tomography (NCCT).

Exclusion criteria: Patients with large territorial chronic infarcts, contraindications to contrast administration (history of an allergic reaction to contrast), and pregnant patients were excluded from the study.

Baseline evaluation included Age, Blood pressure, Clinical evaluation of symptoms, Duration of symptoms and Diabetes mellitus (ABCD2) score [9], cardiac symptoms, blood glucose, and lipid profile. Each patient underwent NCCT brain to rule out acute infarct, intracranial haemorrhage, or old large territorial infarcts. Total 15 patients who fit the inclusion and exclusion criteria were enrolled. A whole brain CT Perfusion scan was performed on Siemens Somatom Definition Flash 256 slice scanner with scan protocol as shown in [Table/Fig-1].

Scanner	Siemens 256 slice definition flash CT scanner
Acquisition type	First pass/dynamic Perfusion CT
Coverage	10 cm
Slice thickness	5 mm
Cycles	24
Cycle time	1.5 s
Total scan duration	40.17 s
Tube current (mAs)	180
Tube voltage	80
Field of view	200 mm
Contrast	40 mL of non ionic iodinated contrast (370 mg I/mL)
Injection protocol	Intravenous using a power injector at the rate of 5 mL/s via an 18 gauge cannula placed in the cubital vein followed by a saline bolus.
Postprocessing	Done on Syngo Via advanced multimodality workstation (version VB 20) using deconvolution analysis method.

[Table/Fig-1]: Computed Tomography Perfusion (CTP) scan protocol.

Procedure

Using an automated threshold-based deconvolution algorithm, colour maps were generated for the CT perfusion parameters-Cerebral Blood Volume (CBV), Cerebral Blood Flow (CBF), Mean Transit Time (MTT), and Time to Peak (TTP). Visual inspection of colour maps was done for any abnormalities. Quantitative assessment of any abnormal areas detected on colour maps was done for the perfusion parameters. Also, quantitative assessment of perfusion parameters was done using bilaterally symmetrical elliptical Region Of Interest (ROI) placements in the following regions: insular cortex, frontal grey and white matter, basal ganglia, occipital grey and white matter, and cerebellar hemispheres. The laterality of the event was determined based on the clinical presentation. The contralateral hemisphere was denoted as the normal hemisphere.

In addition to the above, every patient underwent evaluation of cervicocepahlic arteries. CT angiographic information for the intracranial arteries was obtained from the perfusion CT dataset and images were interpreted for any steno-occlusive disease. For extracranial arteries, every patient underwent a Carotid Doppler study using a linear high-frequency probe. The presence and degree of stenosis in carotid vessels were determined in every patient.

STATISTICAL ANALYSIS

For statistical analysis, categorical variables were presented in number and percentage (%) and continuous variables were presented as mean±SD (standard deviation) and median. The normality of data was tested by the Kolmogorov-Smirnov test. If the normality was rejected then a non parametric test was used. Quantitative variables were compared using unpaired t-test between the two groups. A p-value <0.05 was considered statistically significant.

RESULTS

Out of 15 patients who were enrolled in the present study, 12 were males. The age ranged from 18 to 65 years old. About 11 out of 15 patients had motor dysfunction and the rest four had purely sensory symptoms. The mean time lapse from symptom onset to CT perfusion scanning was 4.5 days.The detailed clinical information along with the focal perfusion abnormality, if seen on CT perfusion scans is presented in [Table/Fig-2].

Five patients had Focal Perfusion Abnormalities (FPA) visualised on colour maps. [Table/Fig-3] shows the values of the four altered parameters in abnormal areas compared to the values in contralateral/normal areas. The analysis shows predominantly increased CBF and CBV in the abnormal areas with CBF being the most affected parameter. The focal abnormalities correspond to the laterality of the symptoms. Two of these patients had an abnormality in more than one area. Focal Perfusion Abnormality (FPA) is also seen in the left caudate nucleus in form of increased CBF, CBV, and decreased MTT [Table/Fig-4-6] show the scans in two of the patients who had focal perfusion abnormality.

Quantitative evaluation of whole brain CT perfusion parameters was performed in all of the patients using elliptical ROI placements in seven predefined areas in each hemisphere. Mean CBF was significantly increased in the abnormal hemisphere (p-value=0.04) as shown in [Table/Fig-7]. No significant difference was evident (p-value >0.05) between the mean of values for CBV, MTT and TTP observed in the abnormal hemisphere and the control hemisphere in the seven different locations that were evaluated by ROI placement. No significant difference was seen for all the parameters between the normal and abnormal hemispheres in all seven locations as well.

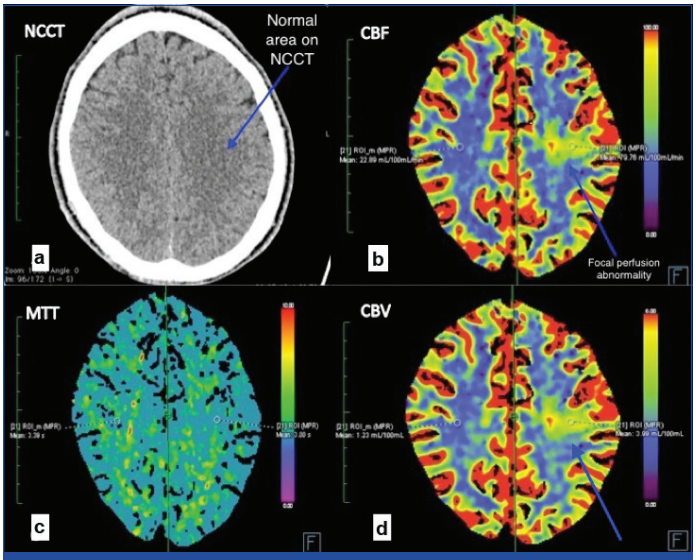
Comparison was done between the complete hemispheric values, gray matter hemispheric values, and white matter hemispheric values in the normal and abnormal hemispheres as shown in [Table/Fig-8-10]. No significant difference was seen on separate analysis of gray matter and white matter. However, the difference in the numerical values of the four parameters shows that CBF and CBV values in gray matter are much higher than in white matter [Table/Fig-8,9]. MTT and TTP values are slightly higher in the white matter compared to gray matter [Table/Fig-10].

Case	Age	Gender	Clinical details	Symptom duration	Time elapsed from symptom onset	Clinical (motor) examination	Focal Perfusion Abnormality (FPA)
1	63	Male	One episode of blurring of vision and dizziness	24 hours	7 days	Right sided mute plantar reflex	None
2	39	Male	Difficulty with fine movements of right hand	36 hours	6 days	Right sided upgoing plantar reflex	None
3	18	Male	Paralysis of right leg with loss of sensation	5 hours	4 days	Power in right ll 0/5 with absent reflexes	None
4	18	Female	Right sided lower limb weakness	12 hours	7 days	Power in right ll 3/5	None
5	48	Male	Inability to speak	2 hours	2 days	Normal	None
6	40	Male	Paraesthesia in right upper and lower limb	10 hours	10 days	Normal	Left periventricular white matter
7	28	Male	Right upper and lower limb weakness	8 hours	7 days	Power in right upper and lower limb 3/5 with absent reflexes	Left lentiform nucleus and left periventricular white matter
8	55	Male	Tongue deviation to right side with difficult in speech	24 hours	1 day	Normal	None
9	65	Male	Right sided paralysis	12 hours	1 day	Power in right upper and lower limb 0/5 with absent reflexes	None
10	59	Male	Left upper limb weakness	14 hours	1 day	Power in left upper limb 0/5 with absent reflexes	Right frontal cortex
11	33	Male	Right upper and lower limb weakness	6 hours	10 days	Power in right upper and lower limb 0/5 with absent reflexes	Left centrum semiovale and body of left caudate nucleus
12	36	Male	Right sided upper limb weakness	2 hours	7 days	Power in left upper limb 2/5	None
13	30	Female	Right sided weakness upper and lower limb	5 hours	2 days	Right sided mute plantar reflex	None
14	50	Female	Left sided tingling and numbness in upper and lower limb	1 hour	1 day	Normal	None
15	63	Male	Left sided paraesthesia in upper and lower limb	2 hours	1 day	Normal	Right thalamus

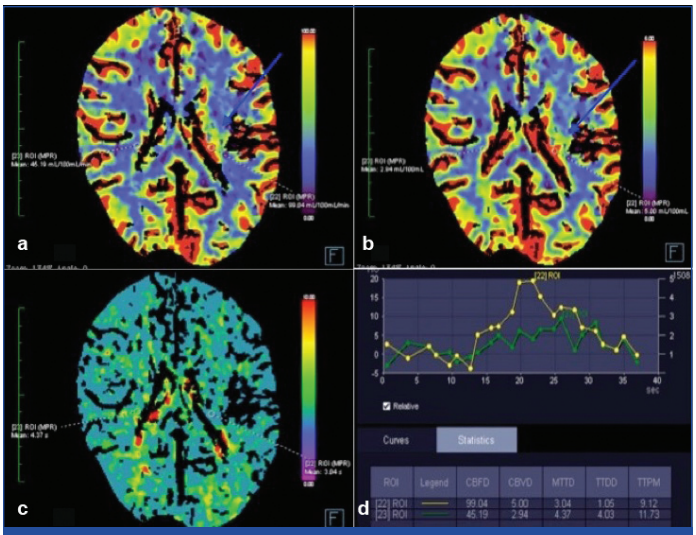
[Table/Fig-2]: Clinical detail of patients.

Abnormal area	Cerebral blood flow (mL/100 gm/min)		Cerebral blood volume (mL/100 gm)		Mean transit time (seconds)		Time to peak (seconds)	
	Abnormal hemisphere	Normal hemisphere	Abnormal hemisphere	Normal hemisphere	Abnormal hemisphere	Normal hemisphere	Abnormal hemisphere	Normal hemisphere
Left periventricular white matter	121.1	45.9	6.7	4	3.6	6	10.3	9.4
Left lentiform nucleusa	177.9	95.6	9	4.8	3	3	7.8	9.4
Right frontal cortex	106.3	63	106.3	63	3	3	10.4	10.5
Left centrum semiovale[b]	79.8	22.9	4	1.2	3	3.4	9.7	11.1
Right thalamus	99.81	78	5	3	3	3	8.3	9
Left periventricular white matter[a]	106.3	93.6	5.4	5	3	3.3	9.1	9.8
Left body of caudate nucleus[b]	99	45.2	5	2.9	3	4.4	9.1	11.7
Mean	112.89	63.46	20.20	11.99	3.09	3.73	9.24	10.13
Standard deviation	31.20	27.20	38.00	22.53	0.23	1.12	0.97	1.00
p-value	0.018		0.018		0.068		0.090	

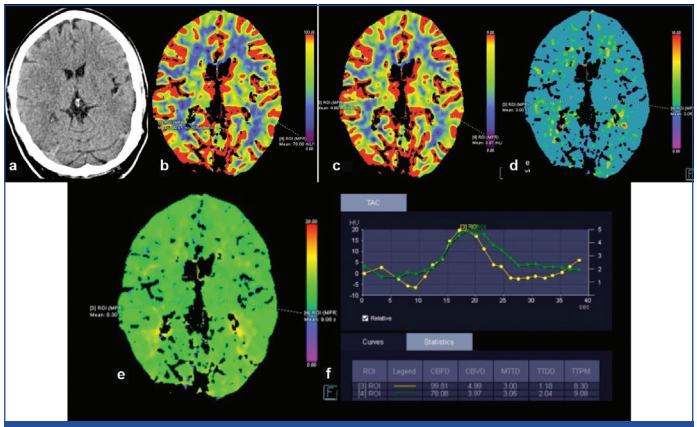
[Table/Fig-3]: Table shows the perfusion parameters [Cerebral blood flow (mL/100 gm/min), Cerebral blood volume (mL/100 gm), Mean transit time (seconds), Time to peak (seconds)] in areas of Focal Perfusion Abnormality (FPA) and their corresponding contralateral normal areas.
[a,b] lesions present in the same patient



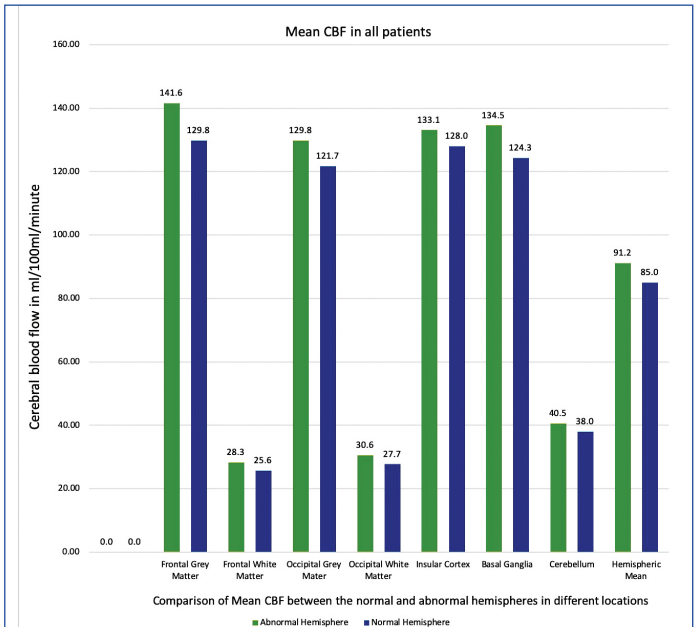
[Table/Fig-4]: A 33-Year-old male presented with right hemiparaesis lasting for six hours. a) NCCT scan shows no evidence of infarction. b)-d) CT perfusion scan shows focal perfusion abnormality (marked with blue arrows in b and d) in the form of b) increased cerebral blood flow (CBF) by 248% and d) increased cerebral blood volume (CBV) by 243% with c) normal mean transit time (MTT) in the left frontal cortex.



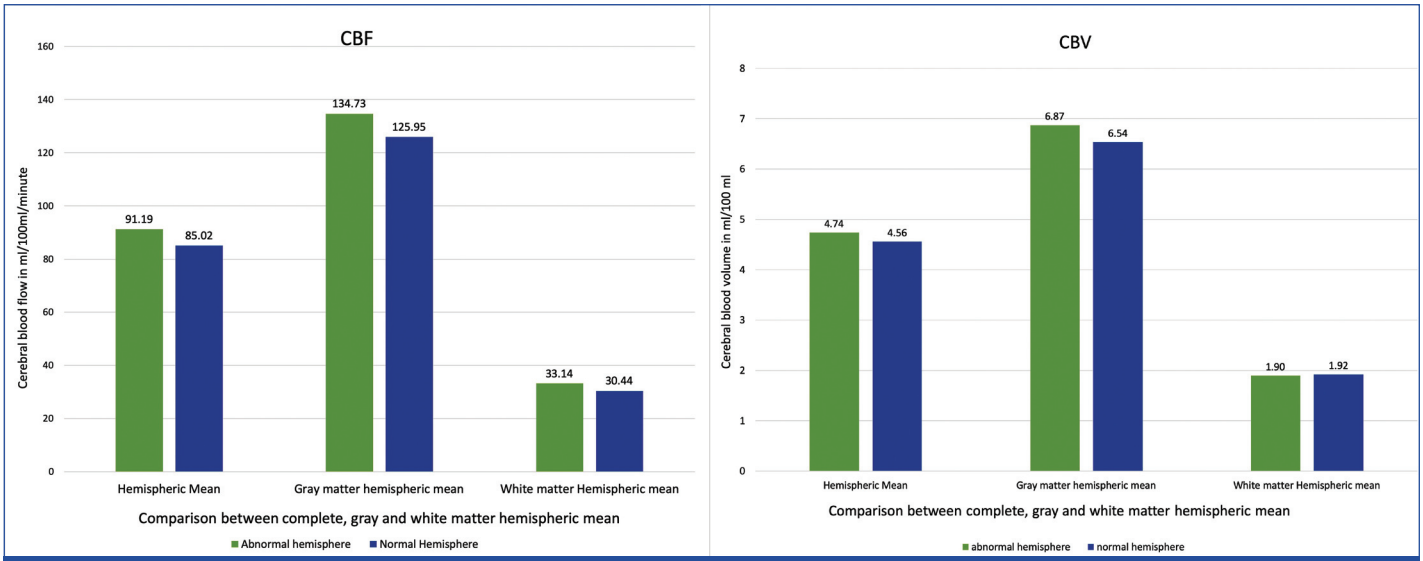
[Table/Fig-5]: In addition to an abnormality in the left frontal cortex region in the patient shown in [Table/Fig-4], focal perfusion abnormality is also seen in the left caudate nucleus (blue arrow) in the form of a) increased CBF, b) increased CBV, and c) decreased MTT. d) The graph shows the time attenuation curve (TAC) for the two region of interest (ROI) drawn on the perfusion maps. The yellow graph shows the TAC for the ROI drawn in the FPA seen in the left caudate nucleus. The green graph shows the TAC for the corresponding normal area in the contralateral right hemisphere. The table below shows the values of individual parameters in these two locations.
TAC: Time attenuation curve, CBF: Cerebral blood flow (unit: mL/100 mL/min), CBV: Cerebral blood volume (unit: mL/100 mL), MTT: Mean transit time (unit: seconds), TTP: Time to peak (unit: seconds), TTD: Time to drain (unit: seconds)



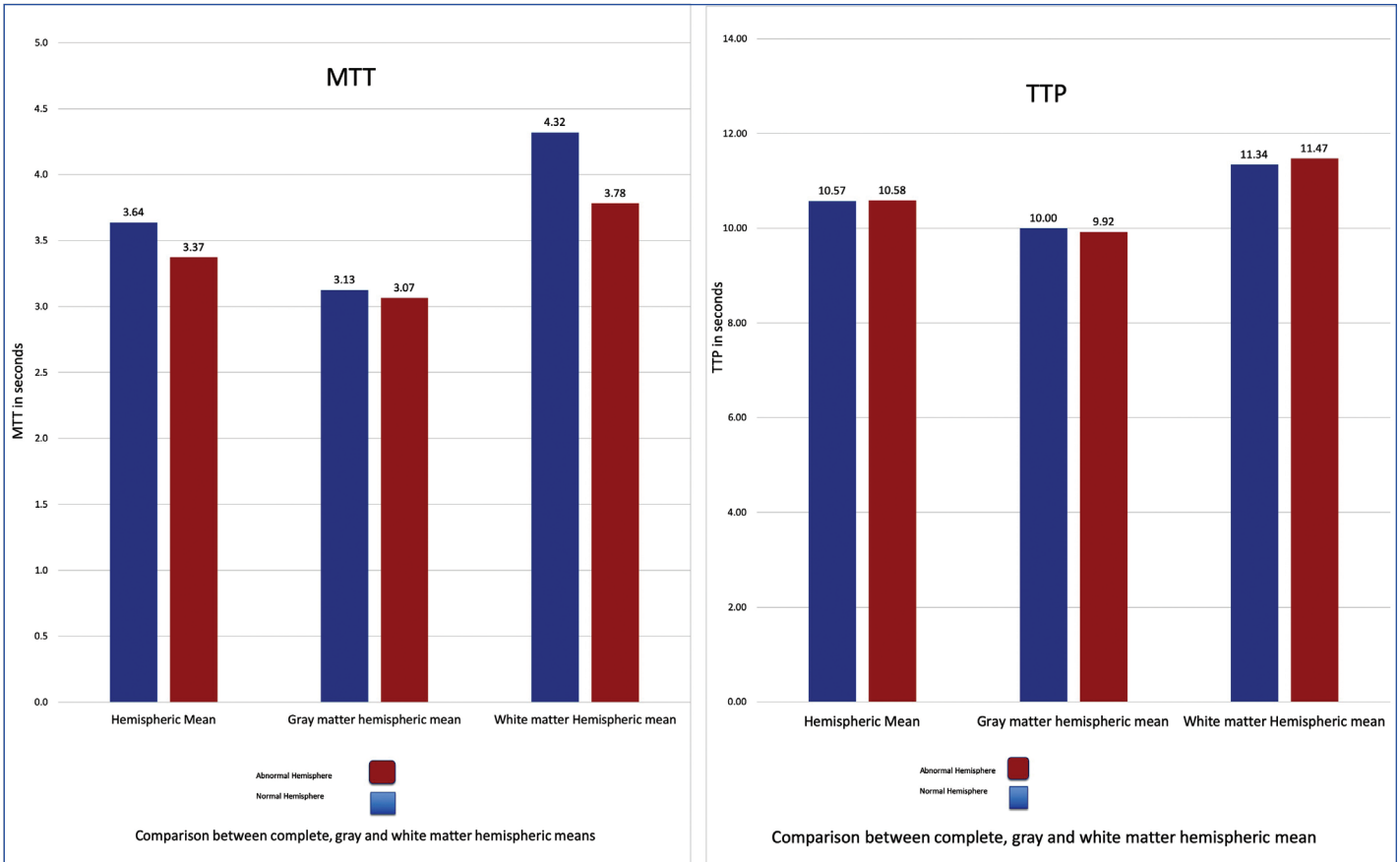
[Table/Fig-6]: Patient who presented with left-sided paraesthesia in upper and lower limb. a) NCCT scan shows no abnormality; b) There was evidence of focal perfusion abnormality in the right thalamus which shows an area of increased CBF; c) and d) show maps of CBV and MTT in the same patient respectively. CBV was raised in the right thalamus whereas MTT was similar on both sides. e) Shows decreased TTP in the area of focal perfusion abnormality in the right thalamus. f) Shows the time attenuation curve for this region (yellow) and the corresponding area in the left thalamus (green) with the values for these areas in tabulated form. The area of focal perfusion abnormality in the right thalamus corresponded to the patient's symptoms of left-sided paraesthesia and showed a pattern of postischaemic hyperperfusion in the form of raised CBF and CBV and decreased TTP signifying recanalisation.
TAC: Time attenuation curve, CBF: Cerebral blood flow (unit: mL/100 mL/min), CBV: Cerebral blood volume (unit: mL/100 mL), MTT: Mean transit time (unit: seconds), TTP: Time to peak (unit: seconds), TTD:Time to drain (unit: seconds).



[Table/Fig-7]: Graphical representation showing the comparison between the abnormal and normal hemispheres of the mean values of CBF in the seven locations and their hemispheric mean.



[Table/Fig-8,9]: Comparison between the complete hemispheric mean, white matter, and gray matter hemispheric mean values of CBF and CBV respectively. (Images from left to right)



[Table/Fig-10]: Comparison between the complete hemispheric mean, white matter, and gray matter hemispheric mean values of MTT and TTP.

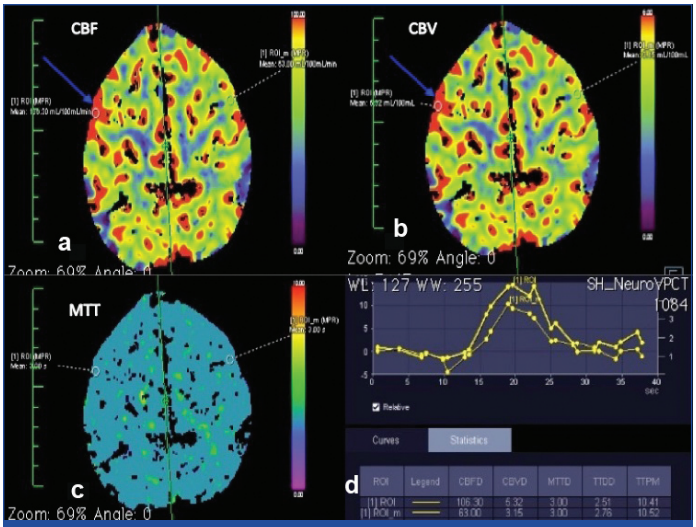
Arterial Evaluation

Six patients had extracranial carotid vessel plaque with significant stenosis seen in two patients. In both the patients with significant vascular stenosis, the location corresponded to the laterality of the symptoms. One of these patients [Table/Fig-11,12] who presented with left upper limb weakness had a focal perfusion abnormality in the right frontal cortex, had a plaque causing 70% stenosis in the right common carotid artery and right-sided MCA (M2 segment) narrowing. The 2nd patient presented with right-sided hemiplegia, had no focal perfusion abnormality, had a plaque causing 80% stenosis in left CCA, and also had intracranial left ICA stenosis with left MCA (M1 segment) narrowing.

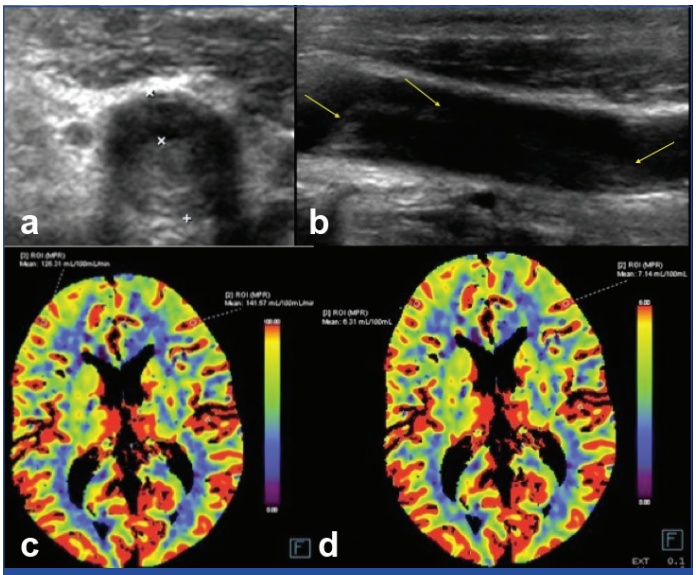
DISCUSSION

The Focal Perfusion Abnormalities (FPA) were found in 5 (33%) patients. Two of these patients had FPAs in two locations. The laterality of these FPAs corresponded to symptomatology. The mean CBF in these regions was significantly elevated compared to the mirror location in the contralateral hemisphere (112.89 mL/100 gm/min and 63.46 mL/100 gm/min respectively; p-value=0.018). The mean CBV in these regions was also significantly elevated compared to the mirror location in the contralateral hemisphere (mean CBV 20.20 mL/100 gm and 11.99 mL/100 gm respectively, p-value=0.018). The difference in MTT and TTP was not found to be statistically significant [Table/Fig-3].

Meyer IA et al., studied focal perfusion abnormalities in patients with TIA and found that of the 265 TIA cases, 110 (42%) had FPA. A total of 107 of these had (97.3%) hypoperfusion, 2 (1.8%) hyperperfusion, and 1 (0.9%) both hypoperfusion and hyperperfusion [8]. In another study, Prabhakaran et al., found that of 65 patients with anterior circulation TIA who underwent PCT, 22 (33.8%) had focal perfusion abnormalities [5]. However, both these studies were based on the old



[Table/Fig-11]: Patient 10: A 59-Year-old male presented with left upper limb weakness lasting for 14 hours. Focal perfusion abnormalities were seen in the form of a) increased CBF by 68% ; b) increased CBV by 68% with c) normal MTT in the right frontal cortex region; d) the TAC and the table below show the values for all the parameters for the two ROIs - [1] ROI is in the FPA located in right frontal cortex region and [2] ROI_m is in the same location in the contralateral normal hemisphere. TAC: Time attenuation curve, FPA: Focal perfusion abnormality, ROI: Region of interest, CBF: Cerebral blood flow (unit: mL/mL/100 ml/min), CBV: Cerebral blood volume (unit: mL/100 mL), MTT: Mean transit time (unit: seconds), TTP: Time to peak (unit: seconds), TTD: Time to drain (unit: seconds)



[Table/Fig-12]: Same patient as in [Table/Fig-11] Patient 10: a) shows the axial Ultrasonography (USG) view of right common carotid artery ; b) shows the longitudinal USG view of right common carotid artery. There is a hypoechoic plaque (marked with yellow arrows in b) in the right common carotid artery causing 70% reduction in diameter (the area between calipers marked as x is the residual lumen). c) and d) show CBF and CBV perfusion maps respectively. No hemispheric asymmetry was seen in these maps.

time-based definition of TIA. The authors observed that five patients out of 15 had focal perfusion abnormalities on CT perfusion. The focal perfusion abnormalities showed hyperperfusion i.e. increased CBF, CBV, and decreased MTT and TTP in these patients. This can be explained by the fact that in the present study CT perfusion was performed after 24 hours in almost all the patients compared to these studies where CTP was done within 24 hours of presentation (median time was 4 hours in the study by Meyer IA et al.,) [8]). Thus, by the time patients underwent CTP in present study, their symptoms had resolved. The hyperperfusion seen in the present study can be explained as Early PostIschaemic Hyperperfusion (EPIH).

EPIH has long been documented in animal stroke models and is the hallmark of efficient recanalisation of the occluded artery with subsequent reperfusion of the tissue. In experimental stroke, early reperfusion has been reported to both prevent infarct growth and aggravate oedema formation and haemorrhage, depending on the severity and duration of prior ischaemia and the efficiency of reperfusion, whereas neuronal damage with or without enlarged infarction also may result from reperfusion (so called "reperfusion injury"). In humans, focal hyperperfusion in the subacute stage (i.e., more than 48 hours after onset) has been associated with tissue necrosis in most instances. However, findings from human studies done with Positron Emission Tomography (PET) imaging suggest that EPIH is not detrimental for the tissue, which contradicts the experimental concept of "reperfusion injury" but is consistent with the apparent clinical benefit from thrombolysis, thus suggesting it is a harmless phenomenon when occurring in the acute setting [10-12].

The mean hemispheric CBF values for the normal hemisphere in the present study were 85.02 mL/100 gm/min. The normal CBF values in the normal adult human brain are reported to be 50 mL/100 gm/min (range 45-55) [13]. Values of CBF are known to be lower in white matter (20 mL/100 gm/min) and higher in gray matter (80 mL/100 gm/min) [14]. This is based on the Kety-Schmidt technique of nitrous oxide washing which is considered the gold standard for CBF determination [15]. Mean CBF values for the entire hemisphere as well as in individual regions are higher than this reference standard in the present study. This difference may be explained due to the different techniques of measurement of CBF in CTP.

Similarly, the analysis of results shows higher numerical values for CBF and CBV than seen in earlier studies on CTP in brain ischaemia/infarction. A study done by Eastwood JD et al., to assess CTP in MCA territory stroke found the mean CBF in full MCA territory in the unaffected hemisphere to be 48.6±10.2 mL/100 gm/min and in the affected hemisphere to be 24.4±13.7 mL/100 gm/min. Similarly, they found mean CBV in the unaffected and affected hemisphere to be 2.7±0.7 and 2.1±0.9 mL/100 gm, respectively. MTT in the unaffected and affected hemispheres was 3.6±0.8 and 7.6±3.8, respectively [16]. Wintermark M et al., in their study to evaluate perfusion CT thresholds for infarct core and penumbra found that relative MTT is the most accurate parameter with a threshold of 145% to define the tissue at risk of infarction. Absolute CBV with an optimal threshold of 2 ml/100g is the most accurate parameter to define infarct core on admission [17]. A study done by Campbell BCV et al., took the threshold value for CBF to determine ischaemia as 24 mL/100 gm/min, CBV was 2.2 mL/100 gm, MTT was 16.6 seconds, and TTP was 9 seconds [18].

Even though in many of these studies the determination of parameters was done using CTP and deconvolution analysis, all of these studies used the earlier generation scanners with limited brain coverage. In our study, the usage of a 256-slice CT scanner providing almost whole-brain coverage (10 cm region) and the use of different postprocessing software can explain the higher values observed for CBF and CBV in all the regions.

A significant difference was seen between the mean of CBF values for normal and abnormal hemispheres with CBF being increased in the abnormal hemisphere. The rest of the parameters showed no significant difference. This increase of mean hemispheric CBF in the abnormal hemisphere can be explained by postischaemic hyperperfusion as already described previously. The analysis on the hemispheric mean values in gray and white matter regions separately shows that the values of CBF and CBV show more difference between the two regions than the values of MTT and TTP. This is consistent with past studies which show less variability of MTT and TTP between gray and white matter and thus MTT and TTP maps are more often used in evaluating ischaemia due to their homogeneity [19,20].

Out of the five patients in whom FPA was seen, only two patients had significant vessel stenosis. This suggests that perfusion abnormality can be seen even in the absence of large-artery haemodynamic compromise. Distal branch occlusive lesions at the arteriolar or capillary level (microcirculation) not visible on non invasive vascular imaging may be operant in these cases [21]. This is consistent with past studies [5].

In both the patients with significant vessel stenosis, no significant side-to-side alteration in hemispheric CTP parameters was seen. In previous studies, the changes in perfusion CT parameters in the setting of significant vessel stenosis are variable. The most consistent change described is MTT prolongation accompanied by variable changes in CBF and CBV [22,23]. This can lead to over estimation of the ischaemic penumbra if the stenosis is on the same side of perfusion abnormality or may mask infarct/ischaemia on the contralateral side [24]. The present study results are different from the above studies. Further studies are required with a larger population size to determine the exact cut-off values for various parameters of CTP in patients with TIA.

Limitation(s)

No follow-up imaging was done in the present study. No Diffusion weighted imaging (DWI) correlation was performed in any patient. The time interval between symptoms and CTP was variable and was not less than 24 hours in any patient.

CONCLUSION(S)

The conclusion of study is that, the CTP parameters are altered in patients with TIA. In patients with focal perfusion abnormalities on CTP, significant increase of CBF and CBV can be seen. Mean CBF is significantly increased in the abnormal hemisphere (hemisphere corresponding to the functional deficit) due to postischaemic hyperperfusion in scans acquired few hours after the onset of TIA. Hence, CT perfusion can be used not just as an alternative modality, but also as a comprehensive imaging method to evaluate patients with TIA.

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PARTICULARS OF CONTRIBUTORS:

1. Senior Resident, Department of Radiodiagnosis, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India.
2. Professor, Department of Radiodiagnosis, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Rohini Gupta Ghasi,
Room No. 6, Ground Floor, OPD Building, Department of Radiology,
VMMC and Safdarjung Hospital, New Delhi-110029, India.
E-mail: rohini1912@gmail.com

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