Analysis of CT perfusion parameters in the setting of cerebral ischemic stroke

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Abstract:
The study was carried out to evaluate the different parameters of cerebral blood perfusion in ischemic areas and to determine the most appropriate parameter to identify infarcted and non-infarcted zone. A prospective study in patients with hemispheric stroke to The Stroke Service over a period of two years was undertaken. Initial CT with CT perfusion and MRI diffusion-weighted imaging was done. Total of 47 cases were studied. NIHSS score was determined. Renal function was done. Time since the onset of stroke as told by the patient or relative was recorded. CT perfusion studies were performed using a 4-slice CT scanner (TOSHIBA) with CT perfusion software. MRI was performed with a 1.5-T clinical whole-body unit. MR DWI images were visually analysed to match the sections on PCT images. The PCT maps and MR images were co registered manually. Statistical analysis used ROC. Mean age was 55.9 years. The Mean NIHSS score was 15.9. Mean CT scan time was 10. 2 hours after symptom onset. The thresholds for rCBF (54%) and rMTT (142%) found would allow differentiation of core and pneumbra. We found a longer MTT with more severe ischemia, in accordance with the central volume principle that states that MTT is inversely related to the perfusion pressure. This statistical analysis of the parameters confirms that rMTT is a better separator of viable and nonviable tissue than is rCBV. Furthermore, higher sensitivity and accuracy were obtained for rMTT than for rCBV and MTT maps. Relative MTT, with an optimal threshold of 142%, provided the most accurate prediction of the final infarct size.

Keywords: CT perfusion, Diffusion MRI, Cerebral blood flow, Cerebral blood volume, Core, Pneumbra, Mean transit time.

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Introduction

Stroke is known to human race since ancient time(1-2). Organized care in a stroke unit has been found to increase the number of patients who survive, return home, and regain functional independence (3-4). So we felt evaluation of a universally available modality that aids in deciding which patient to treat is vital.

Aim of the study

- To evaluate the different parameters of cerebral blood perfusion in ischemic areas.
- To determine the most appropriate parameter and to evaluate the cut – off value to identify infarcted and non-infarcted zone.

Materials and Methods

This is a prospective study that involved adult patients presenting to the emergency room at Rajiv Gandhi Government Hospital with symptoms suggesting hemispheric stroke from April 2012 to March 2013.The diagnosis of stroke was established on the basis of clinical status using NIHSS and CT findings. The protocol for the study was MRI and CT PERFUSION performa. This study protocol was approved by the ethical committee of the institutions and the departmental review board and institutional informed consent guidelines were observed.

Exclusion criteria included:

- Clinical history of prior stroke
- Intracranial haemorrhage on the admission non-contrast CT of the brain
- Standard contraindications to iodinated contrast material
- Standard contraindications to MRI for comparison of their admission PCT with their admission MRI.

Informed consent was obtained by each participating patient and the protocol was approved by the institutional ethical committee. Routine blood investigation to assess the renal function was done. Time since the onset of stroke as told by the patient or relative was recorded.

All CTP studies were performed using a 4-slice CT scanner (TOSHIBA) with CT PERFUSION software. The technique is based on a cine mode continuous acquisition of dynamic flow of contrast. The imaging parameters were 80 kV and 100 mAs, 24 spiral images were obtained. A bolus of 40 ml of the non-ionic contrast material Iohexol 350 (Omnipaque 350) was injected through a 18-gauge cannula placed in the volar aspect in the cubital vein at a flow rate of 4 ml/s. CT scanning was initiated with 5 seconds delay. Sections were selected above the orbits running through the basal nuclei.

MRI was performed with a 1.5-T clinical whole-body unit (Magnetom Avanto; Siemens, Erlangen, Germany). The parameters of multi-shot diffusion-weighted echo planar imaging were TR 3,500 ms, TE 94 ms, 128 x 96 matrix, 230-mm field of view, 5-mm-thick sections with 1-mm interslice gaps, no. of excitations 2, b values of 0, 500 and 1,000 s/mm.

Data was evaluated with commercially available CT PERFUSION SOFTWARE (TOSHIBA). The signal-to-noise ratio was improved using temporal denoising filters for all data (adaptive noise reduction). Vessels were automatically detected and all voxels along the vasculature above a configured percentage of maximum enhancements were excluded from the calculation.

We defined the pneumbra as the difference between the volume with reduced blood flow, as shown at the maps of rCBF, and the ischemic lesion volume at the initial DWI image (ie, the perfusion/diffusion mismatch). Then, 2 regions of interest (ROIs) were placed manually on the perfusion maps. ROI 1 covered the ischemic core, as detected from the diffusion-weighted images. ROI 2 covered the diffusion/perfusion mismatch volume.

PCT data were analyzed using PCT software developed by Toshiba Medical Systems. This software relies on the central volume principle, which is the most accurate for low injection rates of iodinated contrast material. It applies a closed-form (non-iterative) deconvolution to calculate the MTT map (Fig: Image post processing). The deconvolution operation requires a reference arterial input function, selected by us in a region of interest drawn around the anterior cerebral artery in all the cases and the superior saggital sinus was chosen for the venous input function. The CBV map is calculated from the area under the time-enhancement curves. THE CENTRAL VOLUME PRINCIPLE equation combining CBV and MTT values allows the calculation of CBF (CBF_CBV/MTT). Finally, the TTP maps were calculated, indicating the time interval until peak enhancement in each pixel. So CBF, CBV, and MTT were determined with a deconvolution-based algorithm (Fig.1). TTP was determined as the time lag indicated by time attenuation curve (TAC) between the injection of the contrast medium and the local bolus peak in the brain tissue.

The MR DWI reference images were visually analysed to match the sections on PCT images. The MRI reference images were translated and axis orientation as the PCT maps (CBF, CBV, MTT, TTP). The PCT maps and MR images were co-registered.

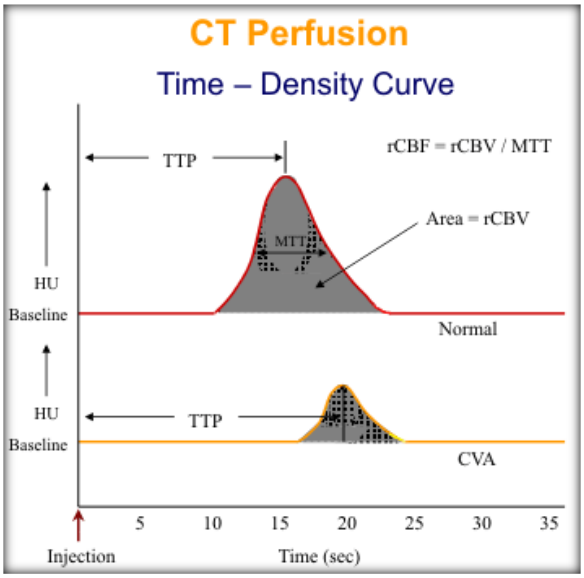
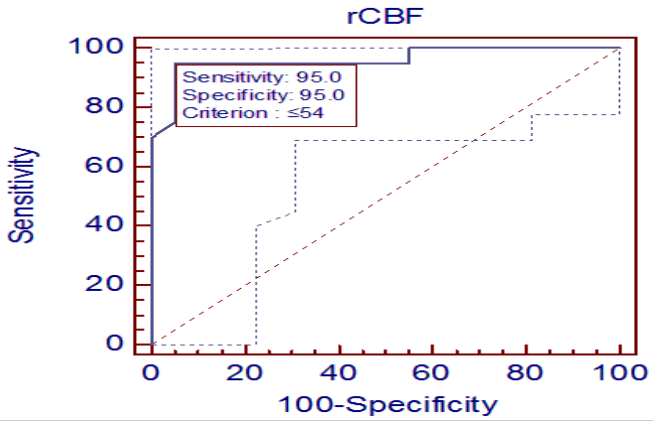


Fig. 1: Time Density Curve

Differences in visually assessed area between the diffusion restriction in the DWI images and the abnormality in the CBF maps indicate the PNEUMBRA. Four absolute parameters were studied: CBF, CBV, MTT, and TTP. Mirrored values were used to generate relative values by dividing absolute value by contralateral mirrored values.

MIRRORED ROI was placed in the region corresponding to the ISCHEMIC PNEUMBRA ZONE and the INFARCTED CORE region to compare the contralateral side to obtain the relative values(Case one - case four).

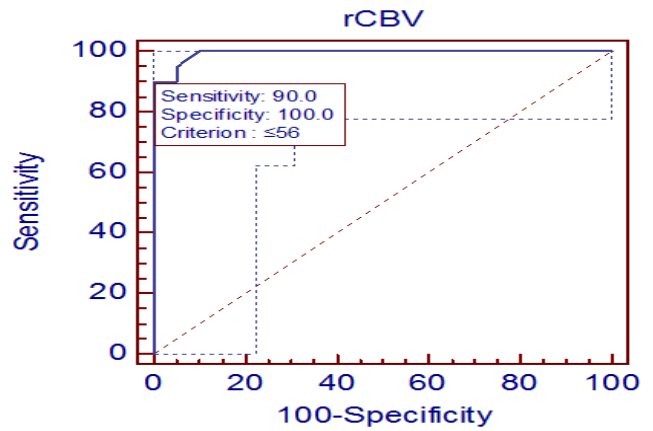
Receiver operator characteristics (ROC): To determine the cut off ratio or threshold relative value of different parameters, which having the maximum sensitivity and specificity. Relative values were used as they avoid interference of different variables like age and blood pressure which can influence the absolute value. Analysis of Variance (ANOVA) - to assess all the four absolute parameters in the INFARCTED and ISCHEMIC group and to find the "F "value and the "P" value which indicates significance (Fig. 2).



Area under the ROC curve (AUC)	0.961250
Standard Error[a]	0.0305
95% Confidence interval[b]	0.901 to 1.000
z statistic	15.119
Significance level P (Area=0.5)	<0.0001

Fig. 2: Receiver OperatingCurve - rCBF

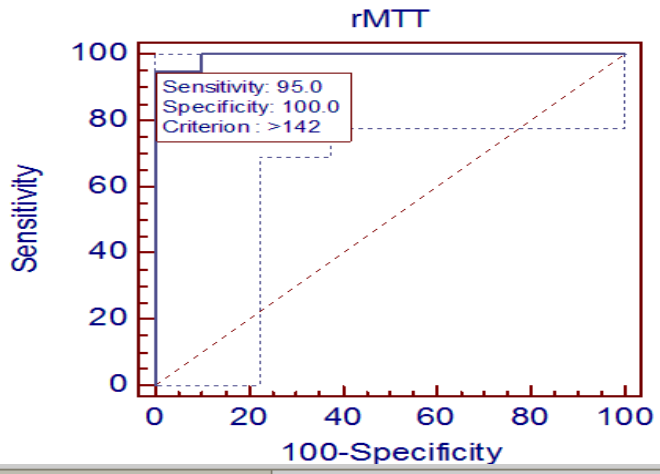
Curve lies in the superior right end of the reference line with SENSITIVITY of 95.0 and SPECIFICITY of 95.0 with a cut -off value of 54**.** Area under the curve indicates significant accuracy with a P value of less than 0.0001 (Fig. 3).



Area under the ROC curve (AUC)	0.993750
Standard Error[a]	0.00673
95% Confidence interval[b]	0.981 to 1.000
z statistic	73.416
Significance level P (Area=0.5)	<0.0001

Fig. 3: Receiver OperatingCurve - rCBV

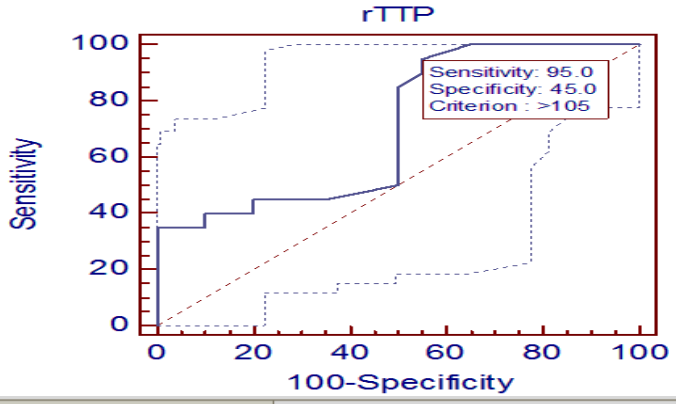
Curve lies in the superior right end of the reference line with SENSITIVITY of 90.0 and SPECIFICITY of 100.0 with a cut -off value of 56. Area under the curve indicates significant accuracy with a P value of less than 0.0001 (Fig. 4).



Area under the ROC curve (AUC)	0.995000
Standard Error[a]	0.00607
95% Confidence interval[b]	0.983 to 1.000
z statistic	81.552
Significance level P (Area=0.5)	<0.0001

Fig. 4: Receiver Operating Curve - rMTT

Curve lies in the superior right end of the reference line with SENSITIVITY of 95.0 and SPECIFICITY of 100.0 with a cut -off value of 142.Area under the curve indicates significant accuracy with a P value of less than 0.0001 (Fig. 5).



Area under the ROC curve (AUC)	0.705000
Standard Error[a]	0.0851
95% Confidence interval[b]	0.538 to 0.872
z statistic	2.408
Significance level P (Area=0.5)	0.0160

Fig. 5: Receiver Operating Curve - rTTP

Curve lies in the superior right end of the reference line with SENSITIVITY of 95.0 and SPECIFICITY of 45.0 with a cut -off value of 105**.** Area under the curve indicates less significant accuracy which is confirmed by a P value of 0.0160.

Table 1: Statistical Data Summary

S. No	Parameter	Sensitivity	Specificity	AUC	Criterion	YoudenIndex
1	rCBV	90	100	**0.99375**	56	0.9000
2	rCBF	95	95	**0.96125**	54	0.9000
3	rMTT	95	100	**0.9950**	142	0.9500
4	rTTP	95	45	**0.705**	105	0.4000

Table1 summarises the efficacy of rMTT to be the most accurate parameter of the four in indicating infarcted and non-infarcted zone with area under the curve is 0.995, and a P value of less than 0.0001.

Results

In this study, forty seven patients were enrolled who were diagnosed to have stroke. All the patients were present within 24 hours after the onset of stroke symptoms. Of these subjects, forty patients satisfied the inclusion criteria after the primary imaging.

In this study, out of 40 patients 31 (77.5%) were males and 9 (22.5%) were females (Figure 6.1) and 10 (25%) patients were in the age group of less than 40 years, 13 (32.5%) patients were between 40 to 60 years of age, 10 (25%) patients were between 60 to 80 years of age and 7(17.5%) were more than 80 years of age. 22(55%) were hypertensive,11 (27.5%) had diabetes mellitus, 8(20%) patients had hyperlipidemia. In 9 patients imaging was taken from 4.5 to 10 hours. In rest of the 31 patients imaging was taken from 10 to 24 hours after the onset of stroke symptoms.

There was a higher rMTT for the infarcted zone compared to the ischemic non infarcted zone. The mean of the two ROIs placed on the core and the pneumbra on the MTT maps differed significantly (1-way ANOVA: F 5.746, P0.005).The cut off value between the pneumbra and core for rMTT was 1.42, with an accuracy of 0.97.This statistical analysis of the parameters confirms that rMTT is a better separator of viable and nonviable tissue than is rCBV. Furthermore, higher sensitivity and accuracy were obtained for rMTT than for rCBV. Infarcted areas demonstrated significant prolongation of MTT values compared with non-infarcted areas (P -0.005).

Discussion

Pneumbra:

The term "cerebral perfusion" implies tissue-level blood flow to brain which is described by a number of parameters - cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT) (1).

Regions which show a CBF between 12 and 22 ml/100 g/min have an unstable metabolic situation in which infarction might develop if low flow persists. PET studies allow the classification into three regions:

1) **Core region of ischemia** - flow of < than 12 ml/100 g/min usually showing a transition into necrosis.
2) **Pneumbra region** - flow between 12 and 22 ml/100 g/min, yet viable tissue with chances to go for infarction or recovery.
3) **Hypoperfused area** (>22 ml/100 g/min) not primarily damaged by the lack of blood supply. They undergo a dynamic change between classes with time(2).

Flow Thresholds for Preservation of Function and Morphological Integrity:

Experiments on ischemic flow thresholds of brain parenchyma have shown there are two crucial levels of decreased perfusion (Fig.6).

1. Level representing flow threshold for reversible functional failure (**functional threshold**).
2. Inferior threshold below which irreversible membrane failure and morphological damage occur.

Fig. 6 shows blood flow cutoff for functional competence and morphological integrity of brain parenchyma. The bold line separates the dead tissue (core) from the rest. Dotted line shows the cutoff below which cell integrity is maintained but action is blocked. Function is restored when blood supply is regained within the time window. This area forms the 'penumbra'.

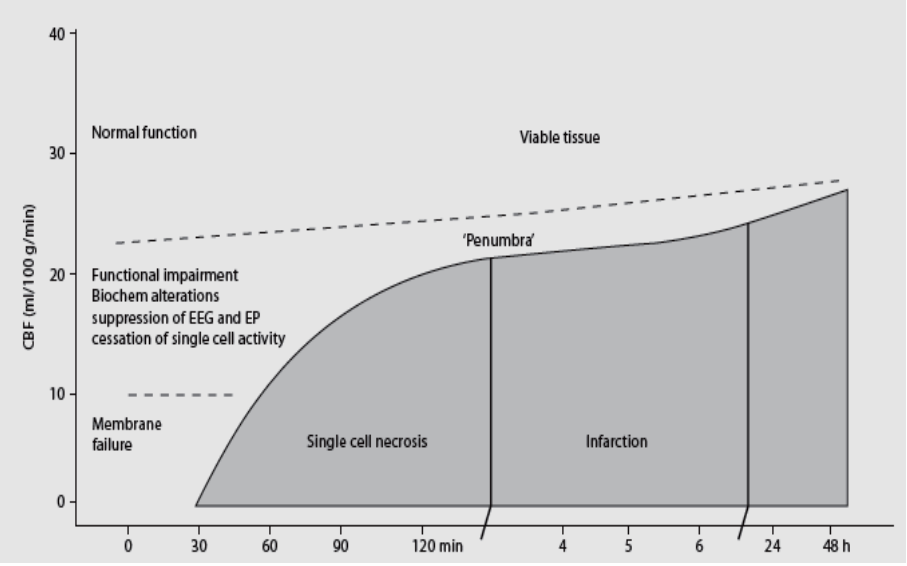


Fig. 6: Blood flow cut off for functional competence and morphological integrity of brain parenchyma

The range of perfusion values between these limits is called the 'ischemic penumbra' which can have functional recovery without morphological damage, only if local blood flow is restored to an adequate level and inside a particular time window. Neuronal function is lost once blood supply decreases below a threshold and leads to development of necrosis and irreversible cell death in a time dependent manner as perfusion is a dynamic process.

Concept of ischemic penumbra (Table 2):
The ability of the brain parenchyma that is functionally quiescent to recover depends on two parameters:

1. Amount of residual flow during the insult
2. Time for which flow abnormality persist.

But, in the extended time window, a good pneumbral pattern is a biomarker of positive outcome since it projects presence of adequate collaterals and increased ability of the tissue to tolerate occlusion(3-6).
Regions with preserved oxygen consumption but reduced flow could be observed around the lesion, at the border zone of the ischemia for up to 24 h or even more(7-8). Juxta - infarct dispersing depression-like depolarisations (PIDs); triggers and stimulates cascade of cell injury (9-10). Waves of PID develop in the pericore or the pneumbra region (11).

Table 2: Perfusion Pattern

	Perfusion	Blood Volume	Mean Transit Time
Autoregulation Range	**Normal**	↑	↑
Misery Perfusion	↓	↑	↑
Ischemia / Metabolic Derangement	↓	↑↑	↑↑
Irreversible Damage/ Necrosis	↓↓	↓↓	↑↑

Numerous absolute threshold values have been proposed for different perfusion parameters in multiple studies. The use of relative values obtained by comparing to the contralateral, uninvolved side can, in part, circumvent the problem of internal bias (12-14). However, even the relative values vary with post processing technique, and the interpreter must be familiar with the software and hardware used (13-14).

Accurate Relative Threshold value:
Using MR PWI and DWI, Schlaug et al identified mean rCBF in the infarcted and non-infarcted ischemic region (operationally defined as tissue that later went on to infarction) to be 0.21 and 0.67, respectively which were found to be in rough agreement with our results of 0.35 and 0.96 for the respective zones ".

In xenon CT and PET studies, infarcted region was found to have a low absolute CBF value (between 6 to 8.43 mL/100 mL per minute). Such low values were possibly due to longer inclusion periods since flow thresholds reduce with time and by differences in methodology (steal phenomenon due to CBF increase in normal luxury perfused areas)(15). Our study also showed similar low values in patients who presented late and all these patients had a high admission NIHSS score and a low ASPECTS score.
In ischemic parenchyma, the first alteration to occur is decrease in cerebral perfusion pressure. This decrease is compensated by dilatation of vessels which leads to an increase in CBV that in turn causes an increase in MTT as per central volume principle (CBV/CBF). But as the perfusion pressure reduces further, the maximum limit of auto regulation is achieved and as vasodilation reaches the limit, CBF begins to decrease further causing CBV to decline. Due to this **bimodal change** in CBV, absolute CBV may not be suitable to interpret in terms of prognostic value. This explains the reason behind CBV being a poor indicator of the ischemic non infarcted (pneumbra) region found in our study.
Winter mark et al(16)showed that increased rCBV denoted a protective effect on the evolving infarction and decrease of rCBV below 0.70,showed irreversible damage, which was in concurrence with our cut off value of 0.56 for infarct and non-infarct region in our study.

Conclusion
We performed a systematic evaluation of all the PCT parameters from data acquired by dynamic CTP–technique in a series of 40 stroke patients. MRI was used as an end point to detect the size of the core (infarcted zone). Our goal was to analyse the different parameters and to find which parameter was the most accurate predictor of infarct and pneumbra. According to our study, it remains uncertain whether increased rCBV has a protective or deleterious effect on the pneumbra whereas rCBV with a cut - off of less than 0.56 indicates irreversible damage. We found a longer MTT with more severe ischemia, in accordance with the central volume principle that states that MTT is inversely related to the perfusion pressure. Since MTT increases monotonically with perfusion pressure whereas CBV changes show bimodal pattern as the perfusion pressure decrease, MTT is an excellent measure of perfusion pressure and the amount of ischemic zone in the affected hemisphere aiding in patient selection for treatment. Our ROC analysis shows that MTT is a more accurate parameter to identify the pneumbra compared with TTP.

Clinical Role: Relative MTT, with an optimal threshold of 142%, provided the most accurate **prediction of the final infarct size** and offered the most accurate delineation of the brain tissue at risk of

dying in the absence of recanalization (ischemic pneumbra).

Limitations: There are some drawbacks in our study. The most serious is one was the use of large ROIs for a voxel-based image analysis to determine the thresholds in the study. Decision making for therapy is based on voxel values and not large ROIs as used in our study. Voxel value analysis needs co-registration which can cause obscuration of thresholds due to alignment inaccuracies and tissue shrinkage. In the present study, we chose a global ROI approach to **establish the existence of perfusion thresholds**. However, in future studies, thresholds found in our study needs to be tested at voxel level on a larger patient sample before they can be applied clinically.

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