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Region of Interest based Multi-parametric Quantitation of Perfusion Weighted MR Images

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Summary

The in-vivo tissue characterization and differentiation of regions of interest (ROI) is an essential constituent of Medical Imaging system. Magnetic Resonance (MR) perfusion imaging is a promising tool for in-vivo study of cerebral hemodynamic perturbations. Analyzing the tracer dynamics and its kinetic distribution offers insight into tissue microcirculatory changes that aid in reflecting the underlying pathophysiology. In our study, we aimed to evaluate region of interest based quantitative measurements of the voxel based derived perfusion indices on stroke and glioma patients and their clinical implications. The resultant information revealed that the hemodynamic variability's on the temporal profile of ischemia can be assessed. The in-house developed software tool employing the algorithm shows the delineation of tumor margin with visible microvascular hotspots and heterogeneity. Thus potentially unravels tumor behavior than is available from feature based extraction of ROI whereby improving diagnostic accuracy and plan of management.

Key words: Region of Interest, rCBV, rCBF, Perfusion Weighted Imaging, Voxel, Algorithm, Microvascular hotspots, Quantitation, Software.

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Introduction

Intrinsic multiparameter dependence is a peculiarity of MR images, which provides high soft tissue contrast flexibility, increased resolution amongst imaging modalities, a possible source for in-vivo tissue characterization. Clinical evaluation and validation of tissue characterization can, however only be derived from quantitative measurement of physiological and functional parameters involved, along with relevant, biochemical, and histopathological correlation. Region of Interest based techniques and software tool are a prerequisite for analysis methods, which plays vital role in discriminating a pathological lesion and normal tissues.

The understanding of pathophysiological basis of stroke has tremendously advanced in the recent past. However, a vast majority of stroke patients are not privileged with an effective treatment, partly due to diagnostic limitations that detect stroke etiology and to differentiate infarct from other entities which may mimic stroke. Magnetic resonance imaging coupled with MR angiography are progressively replacing other imaging modalities for evaluation and screening of stroke. Diffusion Weighting Imaging DWI is highly sensitive, detecting within 3-5 minutes of the onset of stroke, however it suffers from T2 shine through effect and subsequent pseudo normalization limiting its utility in assessing therapeutic efficacy. Also in the case of glioma, the common highly vascular brain tumor, the conventional MR techniques are non specific due to difficulty in differentiating tumor margin and grading.

The role of tracer dynamics offers insight into the distribution of kinetics of contrast agent in the tissue, notably in the case of mechanism that affects cerebral perfusion and tissue characterization. In vivo measurement of microvasculature is the recent focus on evaluation of intracranial mass lesion. There is an increasing demand for both sensitive and specific diagnostic measures of user-friendly defined ROI to characterize healthy from abnormal pathological tissue as well as to assess the efficacy of newer therapeutic interventions. Recent advances in newer imaging MR techniques such as Perfusion Weighted Imaging(1) offers insight into patho-physiological course of infarct, tumor and its relation to treatment response. In our study we aimed to evaluate Region of Interest based quantitative measurements of the voxel based derived perfusion indices (relative cerebral blood volume and flow) on stroke and glioma patients using in-house developed software tool techniques and their clinical implications.

Material and Methods

MR Scanning Protocol - Stroke

Patients (n=7, 5 males, 2 females age range 40 to 65) with acute hemispheric stroke with the presence of main territory or its major branch infarction, restricted diffusion as evidenced by the apparent diffusion coefficient (ADC) values of less

than 0.6 x 10^{-3} mm^2 /sec within range between 22-58 hrs (mean=29.16hrs) from the onset of symptoms were included for the study. Presence of hemorrhage as evidenced by MRI was excluded from the study. Clinical outcome was assessed by using the National Institute of Health Stroke Scale (NIHSS) on the baseline and 7th day after in-patient treatment. Informed consent was obtained from the patient or the nearest kin.

MR imaging was performed on a 1.5-T whole-body scanner (Signa; General Electric Medical Systems, Milwaukee, WI, USA) equipped with echo-planar imaging data acquisition capability. Baseline MRI scans included axial T2-weighted, T1-weighted, fluid attenuated inversion recovery (FLAIR), DWI, perfusion weighted imaging (PWI), and intracranial magnetic resonance angiography (MRA) sequences. Follow-up on treated patients on 7th day MR scans include T2, T1, FLAIR, DWI, PWI. The DWIs were acquired using 5 mm slice thickness with no inter slice gap, field-of-view (FOV) of 240 mm, along with b-values of 0 and 1,000 sec/mm^2 for the calculation of the ADC. Employing single shot spin echo echo-planar pulse sequence, the DSC MR Perfusion weighted imaging was performed with following parameters TR/TE=1900/85, FOV of 30x30 cm, image matrix of 128x128 pixels, slice thickness of 10 mm with no inter slice gap and thirty five phases were obtained in each of 11 slices in 67 sec. After the tenth acquisition, a Gd-DTPA bolus (Gadolinium-Diethylene triaminepentaacetic acid) of 0.1 mmol/kg dose was administered via hand injection(2).

MR Scanning Protocol – Glioma

The present study included histopathologically proven glioma patients (n=25), 15 (mean age = 53) had high-grade gliomas and remaining 10 (mean age = 55) had low-grade gliomas, were subjected to MR Imaging using bird cage quadrature head coil on a 1.5-T MR Scanner. The conventional MRI included T1, T2 and PCT1, followed by DCE MR, employing 3D-SPGR sequence in axial plane with following parameters TR/TE=6.6ms/2 ms, flip angle=15°, the field of view (FOV) = 360 x 270, slice thickness= 6mm, matrix size = 256 x 128. First ten time points were acquired to establish a pre-contrast baseline. At the tenth acquisition, Gd-DTPA in a dose of 0.1 mmol/kg of body weight was administered with the help of a power injector at a rate of 3.5 ml/s, followed by a bolus injection of 40 ml saline flush. A series of 384 images in 32x 12 slices, covering the region of interest, were acquired with a temporal resolution approximately of 7.7 sec for each time point. T2w as well as pre and post contrast T1w axial imaging was obtained for the same slice location chosen for the 3D-SPGR.

Post processing software tool for MR quantitative analysis

All the image data sets acquired from the MR scanner were transferred to a personal computer workstation (Intel-PIV processor, with 512MB). The post processing software evaluation was

carried out using in house software tool developed on IDL 6.0 platform, comprised the following;

- Read Module - Make a 3D volume raw file of all 2D images of any format (Dicom, Siemens, Philips, GE etc) for each MR sequence by removing the header.
- Load Module – Auto loading of each MR sequence (T1, T2, DWI, PWI, MRA) in series to the dynamically referenced locations with options of removing background noise and smoothing of images.
- Registration Module – Automatic Image Registration using specific model (rigid-body, affine or prespective) to align the volume files with provision for manual registration.
- View Module - Creation of MPEG files and navigation capabilities of paging through image sequences or multi sequence cine-mode feature for viewing and slice selection.
- AIF Module - Compare and select voxel based MR signal intensity tissue concentration from 3D image stack for each slice as arterial input function.
- ROI Module - GUI based drawing tools like free hand ROI, lines, rectangles, circular, ellipses etc to compute quantitative features such as total area or volume of each labeled regions of pixels and its mean, standard deviations, maximum and minimum image pixel intensities along with histogram plots within defined ROI's.
- Perfusion Maps Module - To compute Hemodynamic measurements by deconvolving voxel based tissue concentration time curve and generation of rCBV, rCBF, Time To Peak (TTP) and Mean transit time (MTT) maps with provision for overlaid color encode.
- Save Module - Animation and report generation in desired file formats.

For Dynamic contrast enhanced MR pulse sequence, the voxel based 3D SPGR MR signal intensities was converted to tissue concentration time curves C(t) using following expression,

$$c(t) = \left\{ \frac{1}{\alpha} \ln\left[\frac{(S_c(t) - K)}{(S_0 - K)} \right] provided \begin{matrix} S_c(t) - K > 0 \\ S_0 - K > 0 \end{matrix} \right\}$$

where K is defined as the pre-contrast medium steady state residue, which is a non-zero asymptotic quantity that exists in tracer kinetics in the presence of non zero steady state background level and $\alpha = 4.5$ L mmol.s^{-1} is the T1 relaxivity of the Gd-DTPA and the details of these can be found in our earlier reported study(3). While for Dynamic Susceptibilty contrast MR signal intensities were converted to c(t) as reported by Wirestam *et al*(4).

In the in-house developed software, for both dynamic contrast imaging studies the passage of contrast agent through a given voxel of interest $C_{VOI}(t)$ was expressed as the convolution of the

Arterial Input Function (AIF) or $C_A(t)$ with the residue function, $R_{Gd\text{-}DTPA}(t)$, Tissue Concentration $[C_{VOI}(t)]$ = AIF $[C_A(t)] \otimes$ Residue $[R_{Gd\text{-}DTPA}(t)]$ where

$C_{VOI}(t)$ is the measured concentration in the tissue as a function of time on the voxel of interest.

$C_A(t)$ is the tracer concentration in the artery as a function of time.

$\otimes$ denotes convolution.

$C_{VOI}(t)$ is the measured concentration in the tissue as a function of time.

$R_{Gd\text{-}DTPA}(t)$ is the amount of Gd-DTPA tracer present in the vasculature at t.

To study the contrast behavior, the concentration time curve of the tracer was registered in voxel of interest (VOI), selected from the infarct /tumor tissue region, middle cerebral artery (MCA), small artery, white matter (WM) and grey matter (GM) of each slice. To evaluate the functional parameters, we placed number of small ROIs (20-25 pixels) at the lesion site as well on the contra-lateral side and the ratio of these two were subjected to statistical significance. The ROI's were placed over the distinct regions seen on the overlaid color encoded voxels those were fulfilling the characteristics of high range of colors identifying the highest CBV and CBF values.

Non parametric Wilcoxon signed Rank Test was used to analyze the significant changes in lesion volumes, NHSS scores, rCBV,rCBF and MTT ratios in stroke patients and Mann Whitney U Test was applied to Glioma patients. Statistical analysis was performed using SPSS software and p value less than 0.05 was considered significant.

Result

DSC study on Stroke: The rCBV, rCBF, MTT ratios and NHSS score are summarized in Table 1. There was significant increase in rCBF, rCBV ratios; significant decrease in infarct volume and NHSS score but the decrease in MTT ratio was not statistically significant between the baseline and the follow up study.

Table 1

Hemodynamic and clinical parameters of stroke patients on DSC study

Parameter	Baseline (Mean ±SD)	Follow up (Mean ±SD)	p-value
rCBV	0.24±0.18	0.87±0.38	0.005
rCBF	0.12±0.09	0.77±0.5	0.005
MTT	3.37±0.73	0.87±0.57	0.28
Infarct Volume	40.25±9.84	28.83±10.16	0.005
NHSS	12.6±3.36	4.6±1.5	0.005

DCE study on Glioma: MR perfusion maps guided color coded grading of glioma correlated well with histopathological grading. The mean rCBV was 6.47±2.45 in high grade and 2.89±1.47 in low grade and rCBF was 3.94±1.47 in high while 2.25±0.87 in low grade gliomas. A significant difference existed in rCBV and

rCBF values between high-grade ($p < 0.000$) and low-grade gliomas ($p < 0.001$) based on Mann Whitney U test. Two non enhancing gliomas implied a low grade on conventional MRI, but showed high rCBV on generated perfusion maps that correlated with high grade glioma on histopathology (figure 1). In addition, the software tool provided visual appreciation of tumor delination and microvascular hotspots.

Discussion

The in-vivo tissue characterization of different regions of interest is possibly the most important component of a Medical

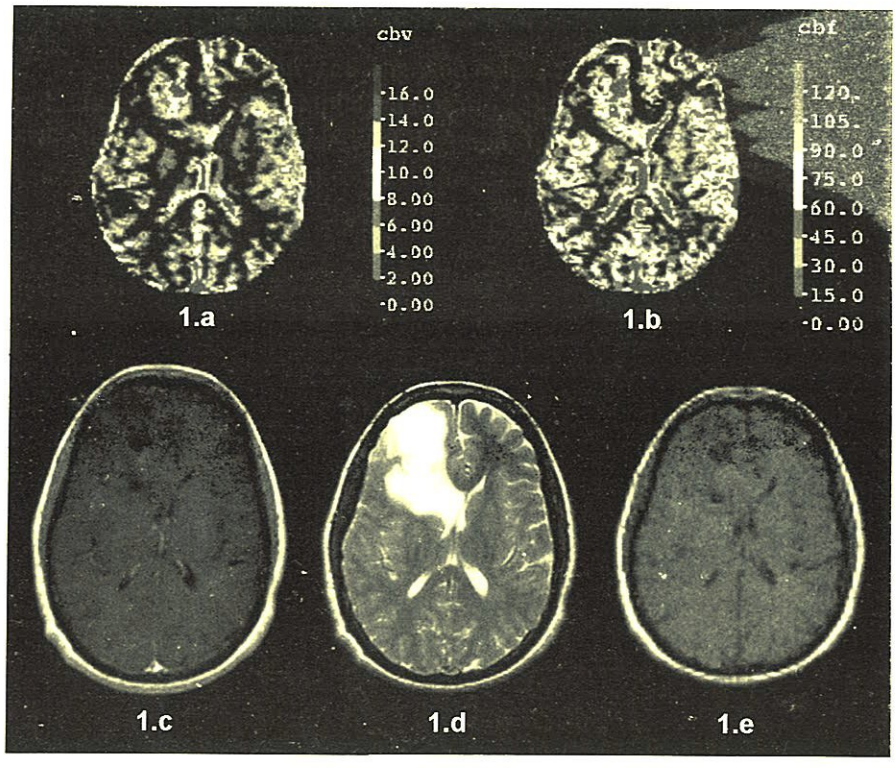

Figure 1. (a) rCBV, (b) rCBF mappings generated for a voxel from 3D-SPGR (c) Post Gd T1 weighted image (d) T2 weighted image (e) Pre contrast T1 weighted image. Non enhancing tumor shows rCBV, rCBF mapping of high-grade lesion (a,b) and Post T1 weighted image (c) demonstrate no enhancement and homogeneity. (a) The CBV mapping demonstrates the vascular angiogenic hotspot with increased CBV in medial aspect of the lesion with surrounding vasogenic edema. Tumor was also present in deep white matter, consistent with infiltrative nature of gliomas. Histology findings prove astrocytoma Grade-III.

Imaging software system. Generally feature based methods require preprocessing of the images to extract features such as edges, landmarks, user defined region of interest and texture. The outlining of complex structures is tedious and often suffers from poor reproducibility. On the other hand voxel based methods work directly on the image gray values without any preceding feature extraction. Even though both approaches have their merits, voxel based methods are more flexible, unbiased and less dependent on the success of the processing steps demonstrating better instant visual appreciation of various tissue characterization.

Although, DWI is highly sensitive in acute stroke, the limitation of pseudo normalization with time may bring illusion on diagnostic accuracy with time and treatment efficacy. Therefore, the evaluation of the perfusion parameters with "user-friendly defined ROI" may aid in assessing temporal profile of stroke and its response to treatment with greater accuracy. The result of the DSC study on stroke patients utilizing the software tool suggests that the changes in relative cerebral blood volume, blood flow and vascular transit time provide information on hemodynamic changes during an ischemic insult, which in particular analyzes the physiology and anatomy simultanseously. It is also of value in detecting and quantifying both immediate and subsequent changes in the hemodynamic state of ischemic brain. However as reported, the potential issues and implications of DSC MR imaging includes T1 shine through effects and nonlinearity of signal changes during Blood barrier breakdown pose underestimation of hemodynamic measurements(1). The identification of therapeutically salvageable penumbra circumventing the limitations will provide a greater scope for the definition of extent of damage and guided therapeutic approach.

Alternatively, T1 weighted Dynamic Contrast Enhanced MR imaging was used to evaluate the hemodynamic parameters in glioma patients that allowed pixel wise analysis of the calculated microvascular components. The non-zero pre-contrast steady state residue was introduced with an aim to overcome the limitations of relative signal intensity that was based on exponential dependence of signal intensity on the T1 relaxation rate in accordance with dynamics of contrast uptake. The results of the study indicated that non-zero pre-contrast steady state residue improved the local linearization between precontrast and post contrast for T1 weighted 3D SPGR technique(3). In agreement with other reported studies, the quantitative measurements of rCBV had good correlation with histopathological tumor grading[5].

Since the MR signal intensity varies for different pulse sequences, the quantitative assessment of contrast uptake primarily depends on respective

pulse sequence parameters(1). The generated hemodynamic maps by deconvolution of voxel based tissue concentration time curve may act synergistically in T1 generated rCBV maps than T2 weighted DSC techniques, whereby the underestimation of rCBV with DSC techniques due to Blood Brain Barrier (BBB) leakage effects are addressed (1, 6, 7). Nevertheless, DCE technique has major limitation on temporal resolution. Further studies are underway to evaluate the underlying mechanisms on tumor delineation.

Advances in image processing methods and application of newer algorithms on medical images are an active area of research with new biomarkers continually being developed for improving diagnostic accuracy and clinical management. The design of software systems must be agile and extensible, that incorporates newer methods without extensive architectural alterations. In the present study, the incorporation of voxel to voxel analysis employing tissue concentration algorithm along with dynamic dual plot of voxel intensity based curves for comparison paved way for modelling the 3D-SPGR MR signal intensities with the effective change in the T1 weighted relaxation rate for each voxel at each time point. As a result the estimated temporal variation of contrast agent concentration time plot before and after administration of tracer Gd-DTPA, guided better generation of hemodynamic maps. The time required for post processing of entire data of a patient is not more than 3 minutes. The in-house developed software tool employing the algorithm provides voxel wise analysis to asses the properties of enhancement curves that offers potentially a far wider range of information concerning tumor behavior than is available from feature based extraction of ROI analysis in terms of vasculature complexity and heterogeneity, showing the delineation of tumor margin from surrounding edematous portion along with visible microvascular hotspots whereby improving accuracy of tumor grading for plan of management.

Conclusion

Quantitative feature extraction of the tissue types or pathological regions of interest based on voxel intensity analysis are a possibility with the developed post processing in-house software tool. The results obtained through voxel based derived methods provide low measurement variability and an increase in confidence in the quantitative end results. These ROI based quantitations on routine images are very useful diagnostic tools that offers diagnostic accuracy for evaluation, planning and monitoring therapeutic management and, could be endorsed using a large data base.

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