Probing Microvascularity and Heterogeneity of Human Glioma using improved T1 weighted Dynamic Contrast Enhanced MRI

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Introduction:
Gliomas are the most common vascularized malignant brain tumors. Measuring changes in tumor hemodynamics would give insight into tumor heterogeneity. The commonly employed Dynamic Susceptibility Contrast suffers from T1 shine through effect. Dynamic Contrast Enhanced (DCE) T1-weighted MRI is a powerful tool capable of providing quantitative assessment of contrast uptake and characterization of microvascular structure in human gliomas[1]. We present an improved T1 weighted Dynamic contrast enhanced MR Imaging employing spoiled gradient recalled echo (3D-SPGR) sequence that provides cerebral perfusion maps for calculation of both rCBV and rCBF, without the additional need of variable flip angles and combines both morphological and functional information during a single imaging MR pulse sequence session. The results have been validated on flow human studies and histopathology.

Methods: Histopathologically proven glioma patients (n=25) were subjected to Magnetic Resonance Imaging using bird cage quadrature head coil on a 1.5-T GE scanner. All patients were subjected to conventional MR Imaging (T1, T2 and PCT1), followed by DCE MR imaging, employing 3D-SPGR sequence in axial plane with following parameters: TR/TE=6.6ms/2 ms, flip angle=15º, 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 seconds for each time point. Prior to this, a 3D-SPGR sequence without contrast was also obtained using the same sequence parameters to study the effects of noise and suitability of algorithm on the resultant cerebral maps. T2 w as well as pre and post contrast T1 w axial imaging was obtained for the same slice location chosen for the 3D-SPGR. The MR signal was modeled in terms of T1 weighted effects of Gd-DTPA. Analyzing tracer behavior on voxel to voxel basis and effective change in T1 relaxation rate[2], a parameter K defined as the pre-contrast medium steady state residue was introduced before converting MR signal intensities into concentration time curve.

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

We developed in-house software for evaluation and generation of perfusion maps rCBV, rCBF[3] by deconvolving Arterial Input Function to calculate residue function[4] using IDL 6.0.

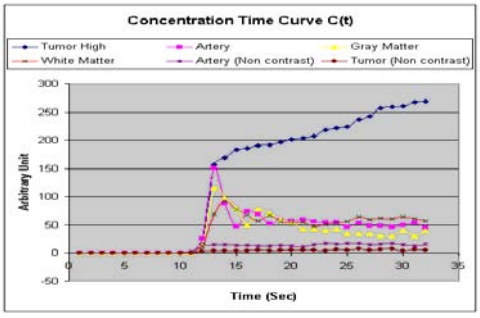

Fig 1. Concentration Time Curve for various VOI

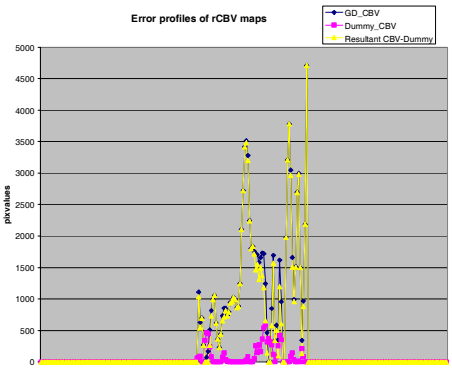

Fig 2. Error profile of rCBV maps

Results: *Concentration Time curve for different voxel of interests (VOI)*: Fig. 1. shows the resulting c(t) obtained from various regions such as artery, within tumor, GM and WM. We found minimal difference in c(t) in selected VOI parts of the brain in without contrast 3D-SPGR study and there was significant difference in the same selected VOI in with contrast study. The minimal signal intensity during passage of bolus was substantially higher than the noise level in all subjects. However an increasing exponential curve is obtained in the tumorous region, represent leaky blood brain barrier (Fig 1.). It also demonstrates that the rate at which tracer bolus appears first in artery, simultaneously in high tumor areas where BBB disruptions occur and are much higher than in GM and WM. The AIF from an artery within the slice through GM and WM were more slightly dispersed than the corresponding AIF from the MCA. 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. Significant statistical difference observed between high and low grade ($p<0.001$). Two non enhancing gliomas implied a low grade on conventional MRI, but showed high rCBV and microvascular hotspots on generated perfusion maps which correlated high grade gliomas on histopathology. The negligible variation (<5%) observed in the concentration time curve (Fig.1and 2.) from the base line of with contrast 3D-SPGR sequence with that of without contrast 3D-SPGR images clearly demonstrates that there is no significant contribution from these physiological and hardware noise factors.

Discussion: The use of 3D-SPGR sequence is well documented. We preferred gradient echo technique than spin echo because of its sensitivity to both capillaries and large vessels. Single-shot EPI pulse sequences often suffer from the severe susceptibility artifacts and distortion which is often worsened when the contrast bolus arrives[1,2]. Various clinical studies have reported the utility of cerebral hemodynamic measurements such as rCBV in differentiating glioma and solitary metastasis. While choosing the AIF, the main consideration is the appropriate shape of the contrast concentration time curve in the plasma, and any inaccuracies in the AIF may lead to errors in both rCBV and rCBF. The SVD based deconvolution method assumes that the AIF into each tissue voxel is known where most of the AIF are approximated by measuring the AIF from the MCA to minimize the error from partial-volume effects. Also the assessment of tracer uptake primarily depends on pulse sequence parameters. The non-zero pre-contrast steady state residue K improves the local linearization between pre-contrast (So) and post-contrast (Sc) for T1 weighted 3D SPGR sequence and the results were consistent in all evaluated subjects. Thus it may overcome the limitations of relative signal intensity. In our study, two of the cases showed no enhancement on post contrast T1 study, implied a low-grade glioma, while the perfusion maps as shown in Fig 3., were suggestive of high-grade tumor; confirmed by histopathology. The equation using K offers insight into tumor grade especially distinguishes non enhancing glioma in terms of high grade including visual appreciation of tumor heterogeneity and the micro-vessel hotspots that correlated with the histopathological report, which is not possible with conventional MR techniques.

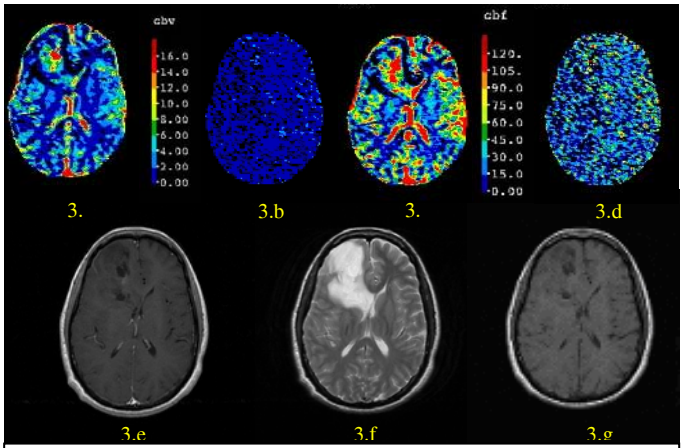

Fig 3. (a) is the CBV and (c) is the CBF maps generated with contrast, (b) and (d) are the CBV and CBF maps generated for the same voxel without contrast 3D SPGR sequence. (e) Post Gd T1 weighted image shows nonenhancing glioma (f) T2 weighted image (g) T1 weighted image (a.) The CBV mapping of non enhancing glioma clearly demonstrates the vascular angiogenic hotspot with increased CBV with surrounding vasogenic edema of high grade nature that correlated with histology findings (astrocytoma Grade-III).

This simple and robust T1-Weighted Dynamic Contrast Enhanced technique improves accuracy of perfusion metrics and enables visual appreciation of micro vascular hotspots; unraveling tumor vasculature complexity, heterogeneity, delineating vasogenic edematous portion from tumor whereby improving accuracy of tumor grading for plan of management.

References: (1.) Jackson A. Br J Radiol 2003;76:159-73. (2.) Rosen BR et al. Magn Reson Med 1990;14:249-265. (3.) Rempp KA et al Radiology 1994;193:637-41. (4.) Wirestam R et al. Magn Reson Med 2000;43:691-700.