

The Utility of the Sequential Contrast Agent Protocol in Assessing *Changes* in Relative Cerebral Blood Volume

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INTRODUCTION Dynamic susceptibility contrast (DSC) experiments measure the MR signal loss induced by the first-pass of a paramagnetic susceptibility contrast agent through the capillary bed. Some DSC experiments have utilized sequential bolus injections of paramagnetic contrast agent to assess changes in relative cerebral blood volume (rCBV) due to perturbations [1]. However, recently the stability and reproducibility of this method for sequential rCBV measurements has been called into question with results indicating artifactually elevated estimates of rCBV with subsequent contrast agent doses [2]. As a consequence of this residual contrast effect, it has been suggested that a relative steady state must be achieved, prior to making any comparative rCBV measurements. This constraint has important implications for the utility of sequential contrast to evaluate *changes* in blood volume which might occur between resting and activated states. In this study, we examine changes in the whole brain CBV as a function of contrast agent dose, for comparison with [2]. We further evaluate the variation of CBV on a voxel-wise basis as a function of dose, and study whether the resting rCBV ratio of gray to white matter changes from bolus to bolus. If not, an *alternate* method for evaluating rCBV changes, in which *changes* in gray matter rCBV may be normalized to white matter rCBV, could be employed for such studies.

METHODS To study the effect of multiple doses of contrast agent, five healthy subjects were studied. CBV was determined with three sequential boluses of Gadoteridol (Prohance®). All images were obtained using a Bruker BIOSPEC 3T imaging system. Interleaved gradient echo (GE) and spin echo (SE) EPI images (64×64, TR=1s, GE TE=27.2 ms, SE TE=110 ms) were acquired in the axial plane at 7 mm thick slices, over 180 seconds, FOV= 24 cm. At 1 minute into the acquisition, 0.05 mmol/kg Prohance® was bolus (approx. 6-8s) injected through a 12-gauge venous catheter. From 5-10 min later, a second injection was given, followed by a third after the same time interval, both 0.05 mmol/kg.

A single whole brain region of interest (ROI) was generated by employing an image mask to remove background noise. The MR signal intensity values were then transformed to the spin echo T2 rate change ($1/\Delta T_2 = \Delta R_2$) and the gradient echo T2* rate change ($1/\Delta T_2^* = \Delta R_2^*$), respectively according to the relation:

$$\Delta R_2^*, \Delta R_2 \propto \frac{-1}{TE} \int \ln \frac{S(t)}{S(0)} dt \quad (1)$$

where, $S(0)$ is the average precontrast baseline MR signal intensity, $S(t)$ is the postcontrast MR signal intensity, and TE is the echo-time. Using the whole brain ROI, an average ΔR_2 -time course was computed for each contrast experiment. The rCBV for the *whole brain* was computed from tracer kinetic theory according to the relation:

$$\text{Whole Brain CBV} = \int_{t_0}^{t_0+12} \left[\frac{1}{N} \sum_N \Delta R_2(t) \right] dt \quad (2)$$

where N is the number of voxels employed when computing $\Delta R_{2, \text{ave}}(t)$; and the rCBV for *each voxel* was computed from:

$$\text{Voxel rCBV} \propto \int_{t_0}^{t_0+12} \Delta R_2(t) dt \quad (3)$$

The initial point t_0 for the integration was determined from a gamma-variate fit to the concentration(ΔR_2)-time image data. The gamma-variate function is defined as:

$$S(t) = Q(t - t_0)^r e^{-(t-t_0)/b} \quad (4)$$

where $S(t)$ is the MR signal intensity, Q , r , b are fit constants, t is the injection time, and t_0 is the appearance time of the tracer. Integration limits were set from t_0 to (t_0+12) points. The Wilcoxon-Mann-Whitney rank-sum test was applied to the rCBV data to determine if there was a significant shift in the rCBV distributions as a function of contrast agent dose. Gray and white matter rCBV maps were generated from

which the ratio, gray rCBV/white rCBV, was computed. Two-way ANOVA was carried out on both, the whole brain rCBVs and the gray/white ratios to determine if there was a significant change in these values for each subject as a function of contrast agent dose. Finally, the above analysis was repeated for one subject after minimizing signal contributions from the large vessels, to enable us to assess the effects of large-vessel contributions on the rCBV distribution as a function of dose.

RESULTS For the range of doses studied, we observed changes in the whole brain CBV as a function of contrast agent dose, similar to previous studies using whole brain [2, 3]. Two-way ANOVA analysis of the whole brain CBV values revealed that they were significantly different from dose to dose, for GE (p-value=0.0319) but not for SE (p-value=0.5783). Mann-Whitney analysis of the GE and SE rCBV distributions revealed that the relative distribution of CBV as a function of contrast agent dose, changed on a voxel-wise basis, for both GE and SE sequences. Two-way ANOVA revealed that the gray/white matter ratios were not significantly different from dose to dose, for both GE (p-value=0.2408) and for SE (p-value=0.7083). The mean ratio for SE was $1.92(\pm 0.37)$ while that for GE was $1.69(\pm 0.37)$. Finally, the same variation of whole brain (GE) CBV was observed as a function of dose, after minimizing signal contributions from the large vessels.

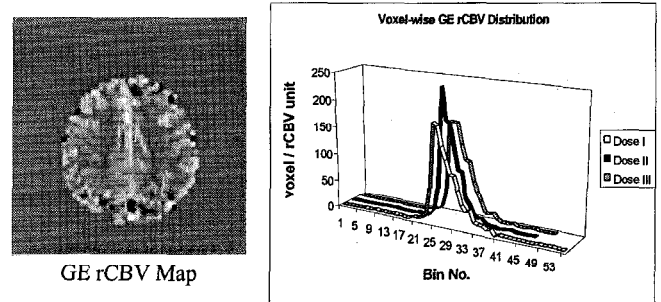


Figure 1.

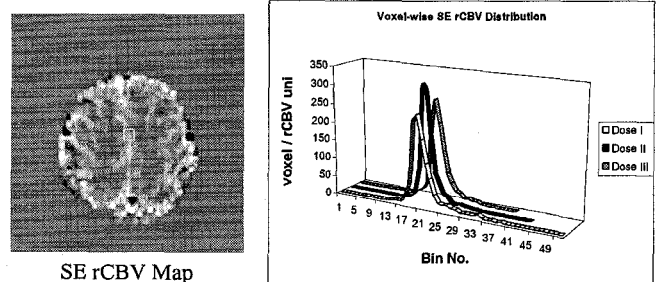


Figure 2.

DISCUSSION/CONCLUSION We have demonstrated that the resting blood volume ratio of gray/white matter stays constant from bolus to bolus, enabling us to evaluate *changes* in gray matter rCBV when normalized to white matter rCBV. Therefore, the utility of the sequential contrast protocol need not be limited to computing the rCBV only *after* attaining a relative steady.

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References

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