Accurate Measurement of Absolute Fractional Blood Volume for the Evaluation of Tumor Angiogenesis

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Introduction: Since the establishment of the relationship between the angiogenic process and tumor growth, accurate assessment of microvascular density became an important issue for many tumor related angiogenic studies[1,2]. However, to measure MVD requires tissue sampling. Though sufficient for diagnosis these methods preclude long term monitoring of treatment. Given the recent development of anti-angiogenic drugs, a non invasive method by which tumor angiogenesis can be evaluated is necessary. MRI methods for measuring tumor blood volume may satisfy this goal.

In the determination of absolute blood volume, blood quantification studies require T1 contrast agents in order to obtain signal responses from the fractional blood volume in tissue. Although close attention has been paid to acquire reliable and accurate signal intensities, the underlying biological conditions and their effects on signal characteristics have often been overlooked, thus resulting in the possibility of gross inaccuracies in the measurement of fractional blood volume (fb)[3,4]. This is especially true when measuring tumor blood volume where the water exchange and the blood inflow as well as the blood volume are expected to be quite different from the normal tissue. It is therefore imperative to eliminate the sources of measurement error by studying the relationship between the different biological conditions and their effect on the fb estimation.

The goal of these studies is to show that Gradient Recalled Echo (GRE) pulse sequences with the parameters insensitive to the biologic conditions (water exchange, inflow) are necessary to minimize the error in absolute volume quantification while enhancing the precision. Our approach is to demonstrate the effects of exchange and inflow upon fb calculation with computer simulations. Secondly, we desire to determine and predict the optimum selection of pulse sequence parameters for the accurate fb assessment independent of exchange and inflow. For the validation of the optimized methods, our final focus is to validate the model with the measurements made in a rat tumor model.

Methods: For the computer simulations, we assumed complete spoiling of the transverse coherences and ignored the geometry of the vasculature. As for the inflow effects, we assumed a plug flow that is always perpendicular to the imaging slice and considered only a rectangular slice profile for all rf pulses used.

The rat experiments were performed on a GE Signa 1.5 Tesla scanner. Four healthy and two brain tumor (9L gliosarcoma) male Fisher rats were cathetherized at both femoral vein and artery for the injection of contrast agent and withdrawl of blood. A body gradient coil with a solenoid extremity rf coil was used to acquire images with a matrix size of 256×128 and TR varying from 35 to 200ms (35, 70, 100 and 200ms) as the flip angle was varied from 10 to 90° (10, 20, 30, 60 and 90°) with slice thickness of 3mm and TE=6.1ms. After the injection of contrast agent, the resultant $T1_{post\ blood}$~250ms. The number of averages varied to take each image within 64 sec. The fb was calculated using no exchange model which assumes that there is no intervascular proton exchange;

$$f_b(No\ Exchange) = \frac{SI_{(posttissue)} - SI_{(pretissue)}}{SI_{(postblood)} - SI_{(preblood)}} \quad [1]$$

Results: The simulation results of the calculated fb for an exchange rate of 3Hz and flow rates of 0.3 and 1.0cm/s are given in Figures 1(a) and (b). In both cases, the fb estimation errors are best minimized when using 180ms<TR<200ms and 80°<flip angle<90° diplaying ~10% overestimation. Upon varying the inflow rate from 0.3 to 1.0cm/s, the error increased by 3% for a flip angle=90° and TR=200ms. The relative range of error at the same flip angle and TR was 15% when increasing the exchange rate from 1 to 3Hz with the inflow set at 1.0cm/s (data not shown). For the range of exchange and inflow rates studied, the best accuracy and relative accuracy using a GRE sequence can be obtained using *a flip angle=90° and TR=200ms* when the contrast agent dose or T1 of the post blood=200ms.

The fb measurements made in the rat brain tissue are shown in Figure 2. The calculated blood volume for normal tissue reveals a strong dependence on flip angle where the fb value decreases with increasing flip angle. A TR dependence of the fb values are also observed. With an increasing TR, the calculated volume increases. However, the measurements mostly coincide at fb=0.025 for a flip angle of 90°. On the other hand, the tumor fb dependence on flip angle and TR is quite different from the normal case (Fig. 2b).

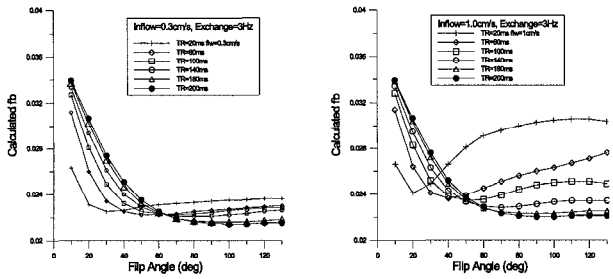

Figure 1: (a) GRE, calculated fb vs. flip angle under the combined effects of inflow(=0.3cm/s) and exchange(=3Hz) with $T1_{postblood}$=200ms, actual fb= 0.02 (b) inflow(=1.0cm/s)

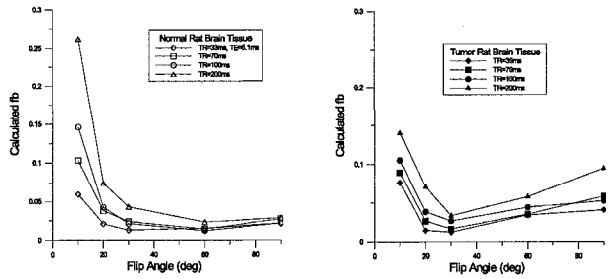

Figure 2: (a) GRE, calculated fb vs. flip angle with no exchange assumptions in normal brain tissue (b) in tumor brain tissue

Discussion: The computer simulations reveal that intercompartmental (intra and extravascular) exchange and capillary inflow rate can significantly influence on the fb measurement. Therefore, in order to minimize the above mentioned effects, it is advisable to use long TR and 90° flip angle when using GRE. The fb measurement variation in rat brain tissue demonstrates the same dependencies which seem to be exaggerated in tumor tissue. This difference may be attributed to inflow and exchange variation. Still, the results correctly indicate a higher tumor blood volume at 90°.

Acknowledgement:

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The enhancing fraction (EF, fraction of tumor voxels with signal enhancement > 50% one minute after contrast agent administration) (19,20) and maps of IAUC60 and the extended Tofts model parameters â€“ Ktrans, ve, and vp â€“ were computed. from the DCE-MRI data.Â From the segmented vessels and tumor masks, fractional blood volume (FBV), vessel surface area normalized to tumor volume (VSA), and median and 90th percentile distances to the nearest vessel (DNV and DNV90) were computed for each tumor.Â Despite the large amount of research on tumor angiogenesis and anti-angiogenic therapy, the mechanisms of action of these drugs are still not fully understood (39). The results presented here reflect this complexity of tumor biology and pharmacodynamics. Ã˜stergaard LSmith DFVestergaard-Poulsen Pet al: Absolute cerebral blood flow and blood volume measured by magnetic resonance imaging bolus tracking: comparison with positron emission tomography values. J Cereb Blood Flow Metab 18:425â€“4321998Ã˜stergaard L Smith DF Vestergaard-Poulsen P et al: Absolute cerebral blood flow and blood volume measured by magnetic resonance imaging bolus tracking: comparison with positron emission tomography values. J Cereb Blood Flow Metab 18:425â€“432 1998. Ã˜stergaard L, Smith DF, Vestergaard-Poulsen P, et al: Absolute cerebral blood flow and blood volume measured by