A Novel Quantification Method for Measuring Vessel Size Selective Blood Volume and Transvascular Water Exchange Rate: Implication of Visualizing Neurovascular Unit

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ABSTRACT Using a large dose of intravascular T1 contrast agent (Gd-PGC[(1)]) and the subsequent susceptibility change in brain vasculature, vessel-radius dependent measurements of various T1-related vascular parameters were proposed. In particular, using the T1 maps of a normal healthy rat brain, a quantification strategy of vascular size-dependent steady state blood volume, transvascular water exchange rate, and limiting effects from extra-vascular /extra-cellular volume fraction was discussed. The heterogeneity of the T1 maps that were affected by intravascular volume and transvascular water exchange rate was highly differentiated between brain tissue types. The results imply that more detailed characterization of vascular parameters in various pathologies (e.g., acute stroke and brain tumor) could be assessed using the dependence of contrast agent-enhanced MR signal intensity on vascular geometry.

INTRODUCTION Local blood volume and transvascular permeability in brain tissue have been frequently quantified for assessing the vascular pathology caused by acute ischemia and tumor. We have previously demonstrated that the absolute blood volume and transvascular water exchange rate could be measured with a large intravascular T1 contrast agent (i.e., Gd-PGC 500kD)[(2)]. Additionally, it could be also suggested that, with an intravenous administration of relatively high dose, the Gd-PGC induces significant changes in intravascular susceptibility in addition to T1 changes, demonstrating a considerable shift in T2 relaxation rate. Due to the vascular size dependence of T2 signal changes (ΔR2) caused by intravascular susceptibility changes, T1-weighted MRI, therefore, could enhance the vessel-size dependent vascular signals using different spin echo times[(3)]. We propose to exploit these features: explicitly, (1) the water exchange rate dependence of T1 relaxation rate and (2) the suppression of vascular size dependent T2-weighted MR water signals with varying TE. Therefore, we introduce a new method that enables one to selectively (i.e., according to vessel geometry) and simultaneously quantify vascular volume and transvascular water exchange rate. The developed technique would quantify how detailed vascular changes occur during the disease progression by emphasizing the relevant vascular structure.

METHODS A healthy normal rat (Sprague-Dawley, 350g) was prepared with a femoral vein cannulation for the administration of Gd-PGC. Prior to contrast agent injection, following MRI protocols were performed using a 4.7T magnet (Bruker). T2 and T2* weighted images were acquired with EPI pulse sequence (TR=8000, Matrix=64x64, FOV=2.5x2.5cm, number of slices/thickness=21/1mm, TE=[9, 14, 20, 30, 40] using gradient echo (GE) or TE=[20, 25, 35, 45, 60] using spin echo (SE)). Inversion recovery echo planar imaging (IR-EPI) was performed with TR/TI=10sec/[10, 30, 60, 100, 300, 400, 500, 600, 700, 800, 1000, 1200, 1500, 2400ms]. The IR EPI images were acquired varying TE=[10, 20, 30ms] with gradient echo (GE) and TE=[20, 30, 40, 50, 60, 80, 100ms] with SE. Following a Gd-PGC injection (170.5μmoles Gd/kg of Gd-PGC), the same MRI protocol was repeated. Additionally, an angiography was acquired using a 3D gradient echo sequence (TR/TE=40/4ms, 256x256x512, and 2.5x2.5x5cm^3). T2 and T2* maps were acquired with a linear least-square fit using Matlab©. For both GE and SE IR-EPI acquisitions and each TE value used, T1 maps were calculated using a three-parameter voxelwise fit (Matlab©) of IR relaxation curve (i.e., $SI(TI)=M_o(1-\alpha\exp(-TI/T1))$. Moreover, the TI data points used for each TE acquisition were varied in order to evaluate the effects of transvascular (intra/extra-vascular) water exchange. Four different T1 fits were calculated, each omitting none, 1st, 1st-2nd, and 1st-4th of TI values used for data acquisition. Multiple ROIs were drawn in regions of cortex, hippocampus, subcortex, and muscle, from which T1 (=1/R1), T2, and T2* values were obtained.

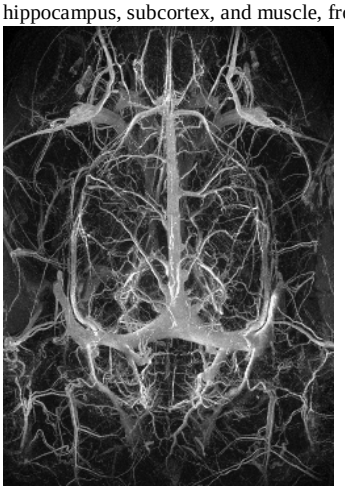

Figure 1. MR angiography of a rat brain using an intravascular T1 contrast agent

RESULTS AND DISCUSSION Figure 1 shows the acquired MR angiography of a rat brain, in which the T1-weighted signal intensity of both arterial and venous blood volume including venous sinuses was highly enhanced following a injection of Gd-PGC. Prior to the Gd-PGC administration, the mean T2/T2* values of cortex, hippocampus, and subcortex were 55.1/62.8, 60.2/57.7, 51.9/40.5ms, respectively. Following the administration, these values were reduced significantly (52.7/49.9, 57.2/47.9, and 49.7/35.5ms, respectively). As expected, with T1 fit without considering shorter TI data points resulted in relatively lower ΔR1 values (Figure 2); that is to say, with increasing the starting TI for T1 fit, most ΔR1 values decreased[(4)] for each TE and echo scheme. The severity of this dependence implies higher transvascular water exchange rate. For the Gd-PGC dose used in this study, a measurement equilibrium appeared to be reached for certain measurement parameters as shown in Figure 2 (i.e., with TI > 60ms for SE TE=40ms in cortex and for GE TE=10ms in subcortex) implying the available interstitial volume for a specific vessel groups[(2)]. Future studies are warranted to resolve the effects of water exchange limited by interstitial space on ΔR1 measurements. As shown in Figure 2 (left panel), for cortex alone, there was a marked heterogeneity in ΔR1 results for SE. Other brain areas (e.g., hippocampus) and muscle showed substantially different measurement dependences (Data not shown). The results suggest that the vessel-size dependent vascular contribution to overall T1-weighted signal intensity is differentiated by choosing different TE and echo methods.

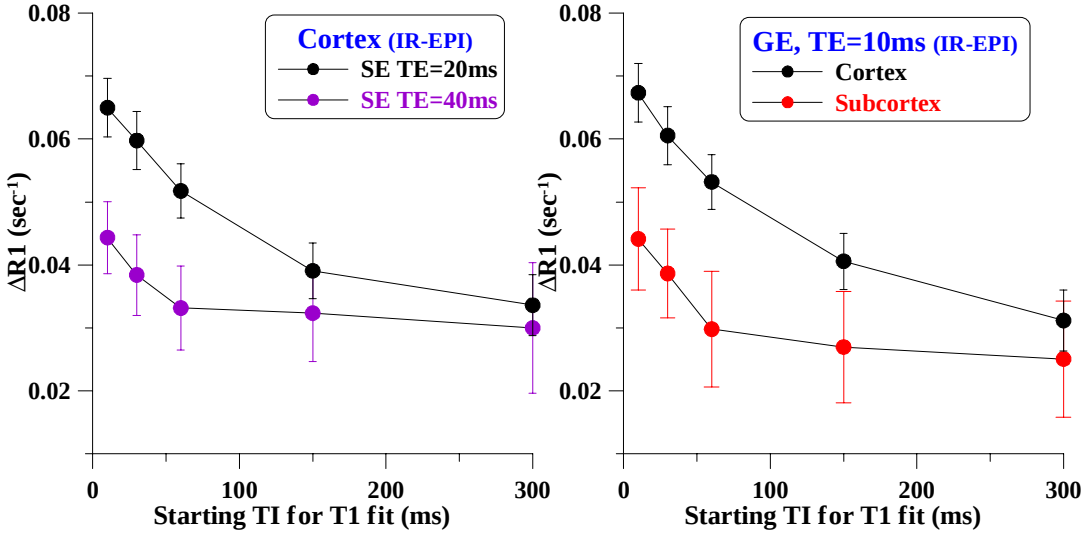

Figure 2. Dependence of T1 relaxation rate change (Δ R1) on TI values used for fit in cortical and subcortical regions for GE and SE varying TE.

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