Intravascular Water Molecule Lifetime in the Japanese Macaque Brain

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Introduction: Non-human primate (NHP) models of cerebral pathology are important for development and efficacy of new treatment therapies.¹,² Interestingly, the remarkable physiological connection between NHPs and humans has not been investigated using dynamic contrast-enhanced (DCE) MRI. DCE-MRI measurements using gadolinium (Gd) based contrast reagents (CRs) are useful for characterizing the blood vessel properties in human brain tissue,³,⁴ and are sensitive to disease-related changes in vascular properties.⁵,⁶ Physiologically important parameters, such as blood-brain barrier (BBB) permeability, blood volume, and transendothelial water exchange have been examined in normal human brain,⁷,⁸ but not in NHP. In this study, we use DCE MRI to investigate BBB permeability (Ktrans), blood volume fraction (v), and the intravascular water lifetime (τv) in Japanese macaque brain.

Methods: All animal care and experimental procedures were IACUC-approved. Ten Japanese macaques (JMs) (4 males, 6 females, ages 7.7-19.6 yr) were selected from a free-ranging colony maintained by our institution. All MR data were collected with a 3T MRI instrument (Siemens TRIO) using a quadrature transmit/receive extremity RF coil. Animals were initially sedated with Telazol, intubated and maintained on 1% isoflurane in 100% O2 during the MRI study. The animals were continuously monitored by pulse oximetry, respiration, and end tidal CO₂. Five full volume parametric [1H]O T₁ maps were produced at different times relative to CR administration by voxel-wise fittings of four consecutively acquired IR-MPRAGE turboFLASH acquisitions (3D TFL: TR/TE = 2500/3.9 msec; FA = 8°) collected with different inversion times (TI = 200, 900, 2000 ms, and also with no inversion pulse). [1H]O T₁ maps were produced by numerically evaluating the Bloch equations for the variable TI data set accounting for all RF pulses and delays with the constraint that each voxel exhibited a monoexponential MR recovery. For DCE measurements, a 0.2 mmol/kg dose of Gd (Gadoteridil, Bracco Diagnostics, Inc) was administered at 0.5 mL/sec using an infusion pump. For each animal, a pre-Gd T₁ map, and four post-Gd T₁ maps were collected at ~6.8, ~17.5, ~28.3, and ~42.7 min. (time values represent the approximate time from CR injection to the acquisition mid-points). The T₁ maps were then masked (performed manually for each animal) to select the entire brain. White matter (WM) and gray matter (GM) T₁ values were obtained from fitting the two prominent peaks in the full volume T₁ histograms to a Gaussian function. BBB Gd permeability was determined as Ktrans (the volume transfer rate constant for CR across the BBB), blood volume fraction as v, and transendothelial exchange was characterized by the mean residence lifetime of the blood water molecule, τv (ms). Ktrans, v, and τv were determined from multi-parameter fittings of the pre- and post-Gd WM histogram R₂[= 1/T₁] peak values to a two compartment model [blood plasma and the extracelluar-extracellular space (EES)] that also accounts for equilibrium transendothelial exchange of molecular water.⁵,⁶

Results and Discussion: Administration of Gd decreases T₁ in WM (Figure 1). The temporal WM T₁ change results from the Gd concentration changes in the plasma and EES (due to nonzero Ktrans) spaces, and also from trans-BBB water exchange. The influence of CR leakage (Ktrans) is shown in Figure 2, where for nonzero Ktrans, the R₂ is elevated at any point in time. Though small, a nonzero Ktrans can result in substantial v and τv errors if they are calculated assuming Ktrans = 0. In one JM, fitting Ktrans R₂ vs. R₁ yielded v and τv values of ~2.8% and ~30ms, respectively, for zero Ktrans, and ~2.5% and ~299ms for Ktrans = 5.5 x 10⁻³ min⁻¹ (Figure 3).

Table 1 lists the uncorrected and corrected (via the group mean Ktrans) v and τv values for each macaque. The mean WM Ktrans (~5.5x10⁻³ min⁻¹) and corrected τv (~300 ms) values in the sedated JM are very similar to Ktrans (~2x10⁻³ min⁻¹) and τv (~260 ms) in conscious humans, whereas the mean JM v (~2.5%) value is somewhat greater than human v (~1.4%)⁵¹. Fitting precision improved after correcting the data for CR extravasation.

Figure 1. Full volume T₁ histogram values and fittings produced from the pre-Gd and ~6.8 min post-Gd T₁ data sets of a 19.2 yr old female macaque. The inset (upper right corner) displays two T₁ maps, the map on the left (A) is a slice from the pre-Gd data, and the map on the right (B) is the same slice from the post-Gd data. The T₁ values in the maps are represented by the grayscale (0-2000 ms) located above the maps.

Figure 2. WM R₂ vs. time. The R₂ data in the graph represent the group mean R₂ values ±SE across the pharmacokinetic time series. Displayed are the curves obtained from fitting the R₂ data to a model that allows for subtle CR leakage across the BBB (Ktrans > 0), and without CR leakage (Ktrans = 0). The difference between the two curves increases with time: The inset (upper right corner) displays the arterial input function [AIF; C(t) (mM)].

Figure 3. WM R₂ vs. R₁ data and fittings obtained from a 16.7 yr old female JM subject. Displayed are the curves obtained from R₂ vs. R₁ fittings of the (uncorrected; Ktrans = 0) R₂ data (●), and the R₂ data (■) corrected for CR leakage (Ktrans > 0). Parameters (v and τv) produced from the fittings are shown in the corners of the figure. The difference between the uncorrected and Ktrans corrected R₂ values with time is proportional to the difference in the R₂(t) curves in Figure 2 (see labels τv, and τv).