First Pass Bolus-Tracking Measurement of Transendothelial Water Exchange in Healthy Controls

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INTRODUCTION. Brain vascular properties are altered in many disease states and measurement of these properties is likely to provide an early and sensitive index of pathology. Low-molecular weight paramagnetic contrast reagents (CR) are commonly employed in clinical MRI studies to identify areas with increased blood-brain barrier (BBB) permeability to CR. The vascular endothelium of the brain is much more permeable to water than CR, and measurements of water permeability could provide complementary and perhaps improved sensitivity to various pathologies. Previously, we measured tissue and blood ^1H_2O R_1 values during the CR washout period and used a two-site exchange (2SX) formalism (1,2) to obtain mean intravascular water lifetimes and blood volume fractions in healthy human brain (1). Measurements that are performed during the CR washout period are susceptible to error if CR extravasation is significant. In addition, such measurements are limited since it is difficult to achieve significant dynamic range in blood ^1H_2O R_1 in physically reasonable imaging times; clearance via the kidneys is rate-limiting. Plasma CR levels can achieve high instantaneous concentrations during the first pass of a bolus-tracking experiment and impart a large dynamic range in blood ^1H_2O R_1 values. Furthermore, the timescale of the first-pass is sufficiently short such that CR extravasation is not likely to be a significant issue except for the leakiest of lesions. The purpose of this study was to investigate measurements of vascular water permeability during CR first-pass in human brain.

METHODS. Data were obtained with consent from five healthy subjects [2F, 3M; mean age (± 1SD) 33 (9) y] using a 4.0 T instrument [Varian/Siemens]. All MR data were collected using a quadrature head coil operating in the transmit/receive mode. Dynamic measurements were obtained using a single-slice inversion-recovery turboflash technique (3). The T_1 recovery was sampled at four times (TI) post-adiabatic inversion with a temporal resolution of 2.5 s. The image matrix was 64^2 over a $(192\ mm)^2$ FOV. A Gauss rf pulse selected a 10 mm transverse slice superior to the lateral ventricles that included a large amount of CSO WM. Antecubital vein catheters delivered boli of 0.05 mmol/kg Gadoteridol (ProHance) at 5 mL/s, followed by saline flushes. The injections began ~20 s after the first frame acquisitions were initiated and lasted ~3 s each. The signal intensity, S(TI), of each voxel was fitted to a two-parameter single exponential IR equation. Tissue ROIs were selected from left and right CSO WM. Each blood R_1 ($\equiv T_1^{-1}$) time-course was obtained from an ROI centered completely within the sagittal sinus. Tissue ^1H_2O R_1 behavior was fitted using the 2SX equation (4):

$$R_1 = \{(R_{1b} + R_{1e} + \tau_e^{-1} + (1\text{-}p_b)/(\tau_e \bullet p_b)) - [(R_{1e} - R_{1b} + \tau_e^{-1} - (1\text{-}p_b)/(\tau_e \bullet p_b))^2 + 4(1\text{-}p_b)/(\tau_e^2 \bullet p_b)]^{1/2}\}/2 \qquad [1]$$

where R_{1b}, for blood ^1H_2O, depends on the plasma CR concentration, τ_e is the average extravascular lifetime of water, p_b = intravascular water volume fraction, and R_{1e} is that for extravascular ^1H_2O in the absence of exchange. Use of Eq. [1] assumes single exponential tissue ^1H_2O relaxation behavior [the fast-exchange regime, FXR (5)] and that there is no significant CR extravasation, which is imminently reasonable in most regions of healthy brain for the first minute following CR injection. Parameter estimates (R_{1e}, p_b and τ_e) were obtained using non-linear gradient expansion methods that fitted Eq. [1] to the average ROI data from each subject.

RESULTS. Figure 1 presents a parametric R_1 map (pre-CR) from a 24 y F with CSO WM and sagittal sinus ROIs indicated. The average R_{1t} time-course obtained from the CSO WM ROIs is plotted in the top panel of **Figure 2,** peaking roughly 17.5 s after CR injection. The R_{1b} time course obtained from the sagittal sinus ROI is plotted in the bottom panel of **Figure 2**. Comparing the R_1 time-course excursions between the top and bottom panels of Figure 2 reveals a significantly damped response in R_{1t} compared to R_{1b}. This non-linear relationship is more apparent in the top panel of **Figure 3,** where the 36 points from the Fig. 2 R_{1b} and R_{1t} time-courses are plotted against each other. Maximum R_{1b} values for the five subjects ranged from ~6 s^{-1} to 8 s^{-1}, sufficient to drive the equilibrium transendothelial water exchange system well beyond the fast exchange limit (FXL). The dashed line indicates the expected response if intravascular and extravascular water system was in FXL throughout the CR passage. The solid line indicates the best fitting obtained using Eq [1]. In the bottom panel of Figure 3 data from all subjects are presented (ΔR_{1t} vectors from each subject were added to mean pre-CR R_{1t} values). 2SX modeling for all subjects is summarized in **Table 1**.

Figure 1

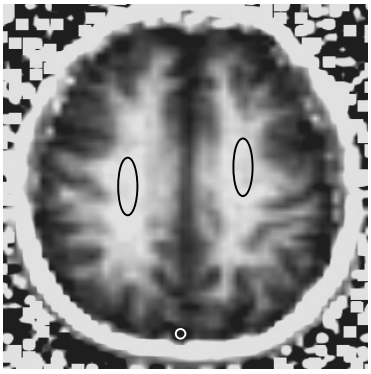

Figure 2

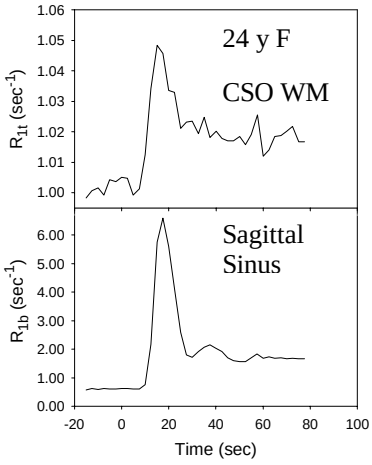

Figure 3

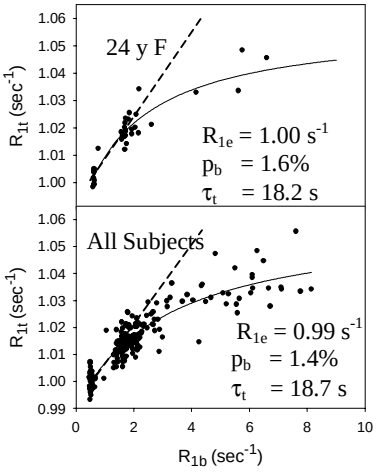

Table 1: Summary of 2SX Modeling

	Age	Sex	R_{1e} (s^{-1})	p_b (%)	τ_e (s)	τ_b (s)
1	24	F	1.00	1.59	18.2	0.29
2	42	M	0.99	1.08	21.2	0.24
3	27	M	1.04	1.26	18.3	0.24
4	45	M	0.91	1.30	18.6	0.25
5	20	F	0.99	1.55	17.3	0.28
mean (± 1SD)	**33 (9.4)**	**3M 2F**	**0.99 (0.05)**	**1.36 (0.21)**	**18.7 (1.5)**	**0.26 (0.03)**

DISCUSSION. The non-linear relationship between tissue and blood water R_1 indicates that the equilibrium exchange system departs the FXL. We have used 2SX modeling to estimate brain blood volumes and transendothelial water exchange dynamics in healthy humans during CR first-pass. The values obtained from this method are in good agreement with previous results (p_b = 1.7%, τ_b = 0.3 s) obtained during the CR wash-out period of ~90 minutes (1). The advantage of the first-pass method is that CR extravasation is much less likely to corrupt the measurement of water permeability even in brain areas with moderately increased BBB permeability. Furthermore, the large dynamic range in R_{1b} achieved allows vascular properties to be characterized for individual subjects.

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REFERENCES. 1. Rooney, Yankeelov, Coyle, Telang, Springer, PISMRM 11:2188 (2003) **2.** Schwarzbauer, Morrissey, Deichmann; Hillenbrand, Syha, Adolf, Noth, Haase. MRM 37:769-777 (1997). **3.** Haase, Matthaei, Bartkowski, Duhmke, Leibfritz JCAT 13:1036-1040 (1989). **4.** Yankeelov, Rooney, Springer, Jr. PISMRM 10:1091 (2002). **5.** Landis, Li, Telang, Molina, Palyka, Vetek, Springer, MRM 42:467-478 (1999).