3T MRI Detection of Contrast Reagent Extravasation in the Normal Primate Brain

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Introduction The detection threshold concentration for a T_1 contrast reagent (CR) decreases with increasing magnetic field [1]. This allows better definition [2] of the hyperfine BALD (Blood Agent Level Dependent) peak at the beginning of the (Dynamic-Contrast-Enhanced) DCE-MRI time-course obtained from the normal brain [3]. The BALD peak can be seen clearly for the human [4,5] and rat [6] at 4T, and there are even hints of it for the human at 1.5T [7]. However, conventional wisdom has it that monomeric Gd(III) chelate CRs do not proceed to actually cross the normal blood-brain-barrier (BBB) in the primate brain. But, gold standard sacrificial studies some time ago found small but nonzero BBB transfer rate constant (K^{trans}) values for the normal rat brain extravasation of two different radiotracers for $GdDTPA^{2-}$ [8,9] (in the earth's magnetic field [10^{-4} T]). Thus, it was reported that BBB crossing of a nonionic Gd(III) CR can be detected in the normal human brain at 4T, with similar K^{trans} values [10]. The purpose of the current study is to investigate both the BALD peak definition and CR BBB crossing detection in the normal brain at the (now clinical) field of 3T. The K^{trans} determination accuracy can be increased by fitting the entire early portion of the DCE-MRI time-course including the BALD peak [3] and, for this very slow extravasation, using a rather long DCE-MRI acquisition period [11].

Methods MRI studies were performed with a 3 T instrument (Trio, Siemens Medical Systems). A six year old female rhesus monkey was used for this IACUC-approved protocol. Anesthesia was induced initially with Telazole (3 mg/kg; Fort Dodge) introduced intramuscularly, and then maintained with 1% isoflurane gas delivered in oxygen. An IV catheter was inserted into a cephalic vein for CR delivery and the subject was positioned supine, head first into a Siemens extremity transceiver RF coil in the magnet. The single slice, fast gradient echo sequence DCE-MRI parameters are: TR 9.8 ms, flip angle 15°, slice thickness 5.0 mm, rectangular FOV 16 x 12 cm^2, 256 read-out points with 75% phase encoding resolution, resulting in an image matrix of 256 x 192. To better detect the first-pass arterial input function (AIF), two Gd(HP-DO3A) (Prohance; Bracco Inc.) injections were used: the first (0.02 mmol/kg) followed two minutes later by a second (0.18 mmol/kg). The first injection started 30 s after commencement of the first DCE-MRI acquisition, which lasted two minutes. A second DCE-MRI acquisition comprised three periods (12, 7, 7 minutes) interspersed with two T_1-weighted 3D image acquisitions. The total acquisition time was ~50 minutes.

Results **Figure 1** shows a DCE-MRI image. The green and rose ovals indicate grey (GM) and white (WM) matter-weighted ROIs, respectively, selected for time-course fitting. An ROI (blue circle) within a tube of aqueous 2mM Gd(HP-DO3A) secured to the animal's head was also selected. The three-site-exchange shutter-speed pharmacokinetic model (BALDERO) [3] was used for fitting the DCE-MRI time-course data. The two fitting parameters were K^{trans} and p_b, the mole fraction ("population") of tissue water in blood. The AIF data were taken from six pixels within the sagittal sinus, and were aligned with tissue time-course data before fitting. The AIF, as $[CR_b]$, is plotted in the **Figure 2** inset.

The circles in Fig. 2 represent the GM ROI time-course data (mean signal intensity divided by that before CR arrival, S/S_0) and the green solid curve the BALDERO fitting. The texture of the fitted curve arises from the numerical integration of the experimental AIF [6]. To better display the BALD peak, two different abscissal time-scales with a break at ~ 2 minutes are used. For the two ROIs, the K^{trans} values are given in the **Table**. The GM- and WM-weighted p_b values returned were 0.019 and 0.017, respectively. Data from the Fig. 1 blue circle ROI yielded S/S_0 values of unity (validated with linear regression) throughout the entire acquisition (not shown), indicating the instrumental stability.

Discussion The results demonstrate that one can indeed detect the hyperfine BALD peak early in the DCE-MRI time-course from the normal primate brain at the clinical field strength of 3T (Fig. 2). Furthermore, one can even analyze the time-course acquired for two-thirds of an hour after the CR injection, and extract K^{trans} values that are consistent with literature values for normal brain tissue (Table). However, the low effect-to-noise ratio at 3T makes it difficult to minimize uncertainties in the parameter values returned. Larger (currently research) magnetic field strengths will greatly assist this type of study in nonhuman, and human, primates [2]. While K^{trans} measures vascular integrity, p_b allows cerebral blood volume fraction, v_b, measurement ($p_b \approx 1.1 v_b$ [3]). The p_b value is mostly determined by the BALD peak [3], from which blood flow can also be extracted [12]. The two p_b values are rather similar here partly because of significant GM/WM partial volume averaging in the large, non-segmented, ROIs used (Fig. 1). The K^{trans} value is largely determined by the shape of the long CR washout tail, and its relationship to that of the BALD peak [3,10]. The Fig. 2 dashed red plot, representing BALDERO time-course for no CR extravasation ($K^{trans} = 0$; $p_b = 0.019$), shows this.

Table

Agent	Tissue	K^{trans} [$[10^{-5}$ (min)$^{-1}$]		Reference
$^{57}CoDTPA^{2-}$	rat brain (n = 31)	1.0 to 2.5 (regional variation)		[8]
$Gd(^{147}Pm)DTPA^{2-}$	rat brain (n = 4)	1.3 to 3.8 (regional variation)		[9]
		GM	WM	
Gd(HP-DO3A)	human brain (n = 11)	5.6	2.9	[10]
Gd(HP-DO3A)	monkey brain	9.5	5.1	this work

Grant support NIH: RO1-NS40801, RO1-EB00422, RR-00163, NMSS RG 3168-A-1.

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