Cerebral Perfusion Imaging with a Hyperpolarized Freely Diffusible Contrast Agent

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Introduction: Hyperpolarized contrast agents have a number of attractive features for application to perfusion imaging [1]. Indeed, these agents provide high signal strength with virtually no endogenous background signal and therefore make excellent tracers for monitoring blood flow. In comparison to arterial spin labeling (ASL), which produces signal modulations on the order of a few percent, hyperpolarized agents should in principle have a significant SNR advantage as well as a slower decay rate to minimize arterial transit dependence. Furthermore, the voxel-by-voxel signal strength from a hyperpolarized agent is simply proportional to its concentration, weighted by a T1-dependent factor. This provides a significant edge over gadolinium-based methods, which suffer from a relatively complex relationship between the flow of blood and the corresponding image contrast. Finally, freely diffusible hyperpolarized agents have significant advantages for cerebral perfusion imaging. In particular, they have a long tissue residence time which allows for the use of slower, more robust imaging sequences than can be used with intravascular agents that have much shorter bolus passage times. Here we describe preliminary studies of hyperpolarized ^{13}C labeled tertiary butanol as a perfusion agent. Fig. 1 shows the structure of t-butanol and the location of the ^{13}C label. The octanol/water partition coefficient of t-butanol is roughly 0.47 [2], implying that it has comparable affinity for lipids and water and should therefore be capable of diffusing through vessel walls and the blood-brain barrier [3]. The agent has low toxicity, with bioeffects comparable to ethanol [4]. Previous work [5] has shown that this agent has a T1 of approximately 48 seconds in blood at 400 MHz field strength.

Methods: Hyperpolarized perdeuterated carbon-13 labeled t-butanol (Isotec, Miamisburg OH) was prepared by combining glycerol and t-butanol in a 60/40 (v/v) ratio. A stable radical ("FINLAND," GE Healthcare, Waukesha WI) was added to a concentration of 15 mM. 236 mg of this solution were placed in a sample cup and transferred to a commercial DNP hyperpolarizer (Oxford Instruments, Tubney Woods, Abingdon UK) and polarized for approximately 3 hours by applying microwaves at a frequency of 94.10 GHz while holding the sample at 1.4K. The sample was then dissolved in 4 ml of EDTA/water (25 mg EDTA/100 ml water) and drawn into a syringe for injection. The polarization level was estimated by polarizing a second sample that was placed in a vial and quickly transferred to a 4.7T animal scanner (see below) for measurement of the carbon-13 spectrum. By comparing with this spectrum with a second spectrum acquired at thermal equilibrium, the polarization level was estimated at 7%.

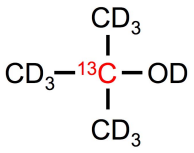

Fig. 1: ^{13}C labeled t-butanol.

During the polarization process a male Wistar rat, weight approximately 250 g, was anesthetized by inhaled isoflurane and a catheter connected to a long tube was placed in the tail vein. The animal was placed inside a linearly polarized proton birdcage coil, and a 2 cm circular transmit/receive carbon-13 coil was placed on its head, directly over the center of the brain. A small vial containing a concentrated mixture of labeled t-butanol in water was placed on top of the coil to enable validation of the coil placement and to aid in calibration of the carbon-13 transmit gain. All animal imaging procedures were approved by the Institutional Animal Care and Use Committee (IACUC).

Imaging was performed using a 4.7T horizontal bore animal scanner (Bruker Biospin, Billerica, MA). Axial T2 weighted proton images were acquired to provide an anatomical reference and to verify the location of the carbon-13 coil. Carbon-13 imaging was performed using a 2D TrueFISP sequence (TR/TE 3.84/1.92 ms, 64x64 matrix, 3 mm slice thickness, 6x6 cm FOV, 8 NEX) prescribed as an axial slice through the center of the brain. Prior to administration of t-butanol, the carbon-13 transmit gain was adjusted to obtain maximal signal from the t-butanol phantom placed on the surface coil; this adjustment is expected to provide maximum signal from the brain following t-butanol administration. After these preparatory steps, 2 ml of hyperpolarized t-butanol solution were administered over a period of several seconds. Approximately 10 seconds after the injection was completed, a single carbon-13 image was acquired using the aforementioned parameters.

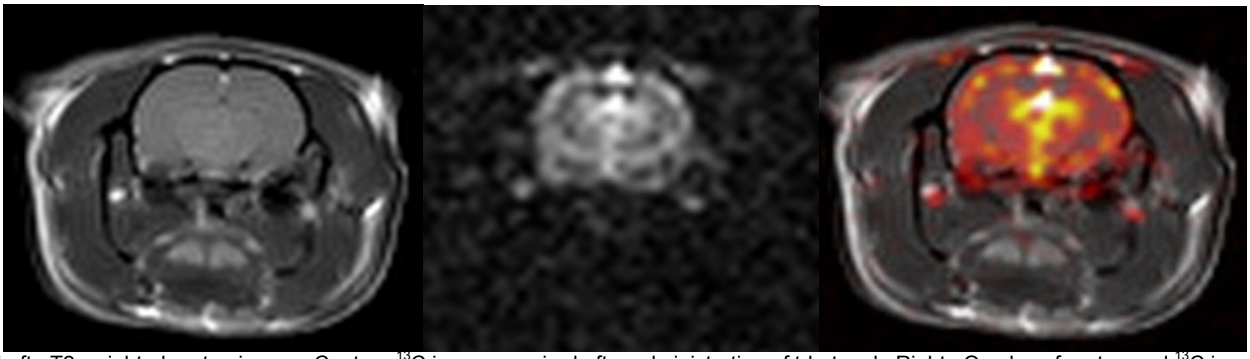
Fig. 2: Left: T2 weighted proton image. Center: ^{13}C image acquired after administration of t-butanol. Right: Overlay of proton and ^{13}C images.

Results: In Fig. 2 we display a proton anatomical image (left) a carbon-13 image, and an overlay of the two images. The carbon-13 image supports the claim that t-butanol is freely diffusible in the brain, as it shows relatively little vascular structure and strong signal after the bolus has already passed. Bright signal in perpendicular large veins probably reflects a time-of-flight inflow enhancement during the 8s acquisition. The SNR of the carbon image, averaged over the brain, is approximately 6.2.

Conclusions: These data demonstrate the feasibility of using hyperpolarized t-butanol for cerebral perfusion imaging. Further optimization of the polarization procedure and the imaging pulse sequences should provide higher SNR and enable dynamic imaging studies. Dynamic methods, in turn, will enable robust determination of cerebral blood flow.

References: [1] E. Johansson *et al.,* MRM 51,464(2004); E. Johansson *et al.,* MRM 52,1043(2004); S. Mansson, *et al.,* Eur Radiol 16, 57(2006); M. Ishii *et al.,* MRM 57,459(2007). [2] S.A. Chicu et al., Quant. Struct.-Act. Relat., 19,227(2000) [3] H.V. Ly and M. L. Longo, Biophys J 87,1013(2004). [4] Int J Toxicology, **24**(Suppl. 2), 1(2005) [5] A Grant *et al.,* Proc. ISMRM 2007, p. 1315.