Freely Diffusible Contrast Agents for Hyperpolarized 13C Perfusion Imaging

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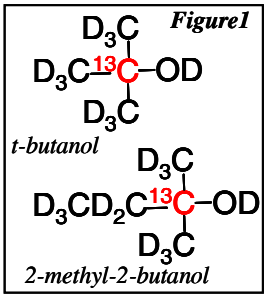
Introduction: Perfusion imaging provides an important tool for the diagnosis and management of many leading causes of morbidity and mortality, including myocardial ischemia, stroke, and cancer. While numerous nuclear medicine, CT, and MRI methods can, in principle, measure perfusion, they are hampered by combinations of limited SNR or resolution, confusion between permeability and perfusion, motion of high background signal, short transit or decay time of the tracer, and nonlinearity of signal response. Hyperpolarized contrast media offer a promising new tool for perfusion imaging. Because these media can be imaged with high sensitivity and essentially zero background, they make excellent tracers for tracking the flow of blood. Perfusion measurement with hyperpolarized Xe has been proposed, but may suffer from limited solubility, anesthetic effects, and shortened T1. Hyperpolarization of ^{13}C agents by parahydrogen induced polarization(PHIP) or dynamic nuclear polarization(DNP) permits the use of a wide range of potential tracer molecules. Previous studies of hyperpolarized perfusion imaging [1] with ^{13}C agents made use of intravascular contrast media. Here we propose the use of freely diffusible alcohols for hyperpolarized ^{13}C imaging. These alcohols may provide significant advantages over previous agents because they can easily penetrate vessel walls, including the blood-brain barrier, and also pass through cell membranes. Because of their high permeability and distribution volume, they will reside in the tissue for an extended period of time, enabling more robust quantification of blood flow in the presence of bolus delay and dispersion. Here we present a discussion of the relevant features of these alcohols, including biocompatibility, diffusibility, relaxation times, and potential techniques for hyperpolarization.

Diffusibility, Concentration Requirements, and Biocompatibility: In Fig. 1 we display two candidate compounds: tertiary butyl alcohol (t-butanol) and 2-methyl-2-butanol. In each case, the quaternary carbon is ^{13}C-labeled and the protons have been substituted with deuterium. As shown below, the quaternary carbon has the longest relaxation time and is the most attractive candidate for labeling. Because t-butanol and 2-methyl-2-butanol have comparable solubility in water and lipids (log of octanol/water partition coefficients are 0.47 and 1.0, respectively,[2]), they can diffuse freely through cell membranes and penetrate the blood-brain barrier [3].



The concentration of t-butanol or 2-methyl-2-butanol required for perfusion imaging can be estimated from the ratio of signal strengths from water and ^{13}C. For any given imaging sequence, this ratio is given by $SNR_{C13}/SNR_H=([^{13}C]/[H])(\gamma_{C13}/\gamma_H)(Pol_{13C}/Pol_H)$, where [X] is the concentration of species X and Pol_X its relative polarization. For 80 molar water at body temperature in a 3 Tesla field, 10 percent ^{13}C polarization (hyperpolarized) and thermal proton polarization, we find SNR_{C13} = 16 $[^{13}C]$ SNR_H. Millimolar concentrations of ^{13}C should therefore be readily observable. The long T_2 relaxation time of ^{13}C and higher polarization will yield further SNR enhancements, which we conservatively neglect here. A 1 mM solution of t-butanol in water corresponds to 0.01 percent by volume. The bioeffects of t-butanol at this concentration are minimal. Indeed, t-butanol and ethanol have similar bioeffects [4], and the legal intoxication limit for ethanol is roughly 0.1 percent by volume--a factor of ten higher than the concentrations contemplated here. For perfusion measurement, such concentrations need only be achieved during first pass, so a dose of approximately 10 mg/kg would be sufficient for many tissues.

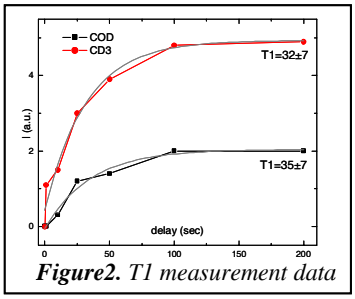


Figure2. *T1 measurement data*

^{13}C Relaxation Time in Blood: The T_1 relaxation time of ^{13}C-labeled t-butanol is a crucial determinant of the feasibility of perfusion imaging. T1 of the quaternary carbon in blood was measured. Blood was obtained from a human volunteer, from whom informed written consent had been obtained, and natural ^{13}C abundance deuterated t-butanol was added to a concentration of 1M. To prevent coagulation, blood was drawn in a heparin-treated vacutainer and 100 mM sodium citrate was added. To slow the separation of blood components, blood cells were lysed using an acoustic sonicator. The solution was placed in a 5 mm NMR tube, and the relaxation time was measured using a saturation recovery technique in a 400 MHz (9.6T) Varian spectrometer. Throughout the experiment, the sample was maintained at body temperature (36^0C) and periodically agitated to maintain blood homogeneity. The median value of T_1 for the quaternary carbon, averaged over 4 experiments, was found to be 64 ± 20 sec, and for methyl carbon 26±5 sec. Representative data for a single saturation recovery experiment is displayed in Figure 2. It is reasonable to assume that other tertiary alcohols will have similar T1s. This data suggests that hyperpolarized quaternary carbon in alcohols can be used successfully for perfusion imaging. The hyperpolarization can be created either via the DNP method or via PHIP and the T1 is long enough for transfer, injection, distribution and imaging.

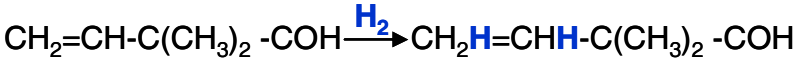


Figure 3. *PHIP hyperpolarization scheme of 2-methyl-2-butanol*

Preliminary Results with Parahydrogen-Induced Polarization: It is possible to prepare hyperpolarized 2-methyl-2-butanol by means of parahydrogen-induced polarization. A scheme for doing so is illustrated in Fig. 3: 2-methyl-3-buten-2-ol is hydrogenated with enriched parahydrogen to form 2-methyl-2-butanol. The feasibility of this reaction is demonstrated by the PHIP-enhanced proton spectrum of 2-methyl-2-butanol displayed in Fig. 4. This spectrum was obtained by hydrogenation of 2-methyl-3-buten-2-ol in a 5mm NMR tube under moderate (~3 bar) pressure using the techniques described in [5]. Although the enhancement is modest, the reaction rate can be improved by means of increased pressure and/or temperature. Moreover, the proton polarization can be transferred to ^{13}C by means of magnetic field cycling [6] or RF pulses [7].

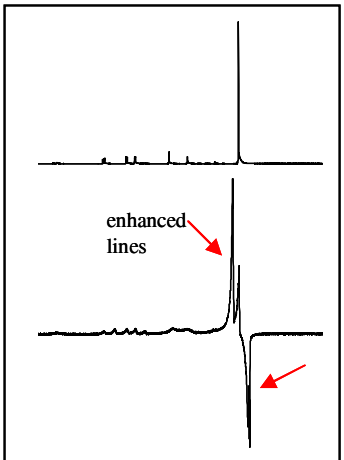


Figure 4. *PHIP enhanced proton spectrum (bottom) and a corresponding spectrum at thermal equilibrium (top).*

Conclusions: Tertiary alcohols, including t-butanol and 2-methyl-2-butanol are attractive candidates for hyperpolarized ^{13}C perfusion imaging. They are freely diffusible in tissue and can penetrate the blood-brain barrier. Furthermore, the T_1 relaxation time in blood is more than adequate to allow for vascular distribution of the contrast medium. The requisite peak concentration of alcohol is roughly 0.01% by volume, which is expected to have minimal bioeffects.

References: [1] S.Mansson, *et.al.,* Eur Radiol 16, 57(2006). [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.K. Grant, *et.al.,* Proc. ISMRM 14, 2552(2006) [6] H.Johannesson, *et al.*, *C. R. Physique* 5, 315(2004). [7] M.Haake, *et al.* J Am Chem Soc 118, 8688(1996).