Multi-Compound Hyperpolarized ^{13}C Perfusion Imaging

Cornelius von Morze[1], Robert A Bok[1], Galen Reed[1], Jan Henrik Ardenkjaer-Larsen[2,3], John Kurhanewicz[1], and Daniel B Vigneron[1]

[1]*Dept. of Radiology and Biomedical Imaging, UC San Francisco, San Francisco, California, United States,* [2]*GE Healthcare, Frederiksberg, Denmark,* [3]*Dept. of Electrical Engineering, Technical University of Denmark, Lyngby, Denmark*

Introduction- Perfusion images reflect tracer physiology, as molecular structure dictates the biodistribution of the contrast agent. Dissolution DNP[1] has enabled development of three hyperpolarized (HP) ^{13}C perfusion tracers (Fig. 1), based on the key criteria of high polarization enhancements, long T_1, negligible metabolism, and low toxicity: [^{13}C]urea[2] (T_1=47s in solution at 3T, δ= 163ppm), [^{13}C]HMCP[3] (hydroxymethyl cyclopropane aka HP001, T_1= 95s, δ= 23ppm), and [^{13}C]t-butanol[4] (T_1=46s, δ= 70ppm). As a result of their dissimilar molecular structures, these tracers exhibit widely different distributions *in vivo* due to varying bilayer permeability and transport, and have wide spectral separation. Urea (log K_{OW}=-2.80) is highly polar and has correspondingly low bilayer permeability, while t-butanol (log K_{OW}=0.35) is "freely diffusible". Urea however is rapidly transported across cell membranes in red blood cells and the renal inner medulla[5,6]. To obtain an unprecedented level of physiologic detail in perfusion imaging, we have co-hyperpolarized[7], injected, and simultaneously imaged these three "tri-polarized" tracers. To overcome the poor speed of traditional spectrally selective imaging (e.g. CSI), we applied bSSFP imaging[2,3] with rapid spatial-spectral readout by multi-band frequency encoding[8] (MBFE). We capitalized on wide, regular spectral separation to achieve simultaneous dynamic imaging with full body coverage in preclinical murine imaging studies, using MBFE and bSSFP with ramped flip angle. We modeled the data with direct signal proportionality to tracer concentration to estimate absolute perfusion parameters. Our methods may be useful in tumor imaging for isolating vascular and perfused tissue compartments, and separating vascular permeability and perfusion, which are difficult to separate but have unique implications with respect to therapy.

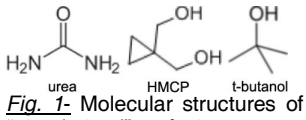


Fig. 1- Molecular structures of "tri-polarized" perfusion tracers

Methods- *Pulse sequence design:* Since the spectral separation of HMCP&urea (4495Hz) is nearly an exact integer multiple of HMCP&t-butanol (1497Hz), a center frequency near HMCP and a TR of an integer multiple of 1/1498 Hz (18.0ms) results in replication of the on-resonance SSFP response for all compounds to within ±1Hz. A usable bandwidth of 16Hz (~0.5ppm) was obtained for each compound, where signal variation as a function of frequency and oscillation over phase encodes was <10%. While this TR is prohibitively long for ^{1}H SSFP at 3T due to banding, because of the lower γ of ^{13}C it is equivalent in terms of artifact level to 4.5ms for ^{1}H. These shifts were also used to set up the modified readout filter (6.0kHz) and reconstruction pixel shifts for MBFE, and to compensate for tilted excitation profiles. Excitation was by a sinc pulse (2.63ms), with dynamically increasing flip angles α= 0.5°, 1°, 2°, 4°, 6°, 9°, 12°, 16°, 20°, 25°, 32°, 41°, 55°, 70°, 100°, 130°. *Hyperpolarization:* For each study, 0.5 mmol of urea, HMCP, and t-butanol were loaded into the sample cup of the Hypersense, with freezing by immersion in LN_2 at each stage. Dissolution in 4.5mL PBS yielded an equimolar 110mM solution. *MRI Experiments:* A normal rat and 3 transgenic mice with prostate cancer[9] (TRAMP) were imaged. Each mouse was injected over 12s with 350μL, rat= 2.4mL. The nominal spatial resolution was 2.5mm x 2.5mm x 10mm. Dynamic multi-slice imaging commenced at the start of injection and was repeated every 3.8s over 57s. Three extra slices were added to one end of the stack to account for tilted transmit profiles. *Data analysis:* Key anatomic regions were manually defined on T_2 images. Corresponding dynamic curves were generated, and image-derived arterial input functions (AIF's). Perfusion modeling[10] was by non-linear fitting of $C_{tissue}(t) = F \cdot exp(-Ft/V_T + \lambda) \otimes C_{blood}(t)$ where C_{tissue} is the tracer concentration in tissue (MR signal / mL tissue), C_{blood} is the arterial input function (MR signal / mL blood, input vessel size determined from ^{1}H time-of-flight MRA), and λ is the tracer-specific decay rate (s^{-1}) in the ramped flip angle scheme, while *F* is the jointly estimated tissue blood flow (mL flow / mL tissue / s), and V_T is the tracer distribution volume (mL/mL). Due to impermeability of red blood cells to HMCP, its AIF was corrected for hematocrit.

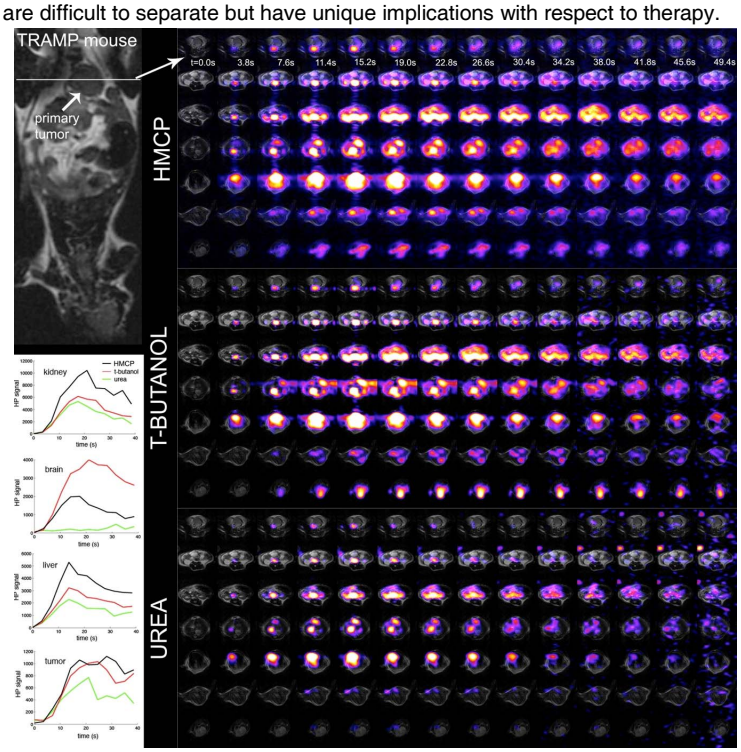


Fig. 2- Axial, tri-polarized dynamic perfusion curves (bottom left) and images (color) in TRAMP mouse, overlaid on T_2-weighted FSE images.

Results and Discussion- No effects on heart rate or respiration were observed. Due to the periodic SSFP frequency response, all compounds were excited. Component images appeared side by side along the frequency dimension. A full set of dynamic images is given in Fig. 2. Images revealed interesting differences in the distributions among the three tracers. T-butanol is freely diffusible in brain, while urea crosses the blood brain barrier only 240x slower than water[10], so simultaneous imaging of these tracers isolates cerebrovascular and perfused brain tissue compartments (Fig. 3). Tumor blood flows and distribution volumes (Table 1 & Fig. 4) were elevated vs. normal tissues, consistently with prior "blood flow" PET studies[11]. Tracer distribution volumes generally increased with increasing diffusibility. Quantification of tri-polarized data is promising because of high extraction and direct proportionality of signal to tracer concentration. It may be possible to separate effects of vascular permeability and perfusion based on the tracer V_T's.

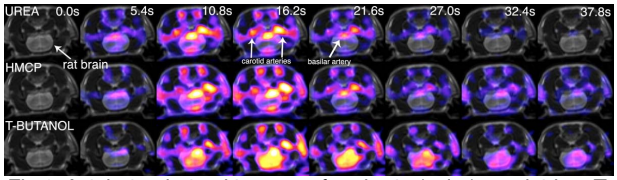
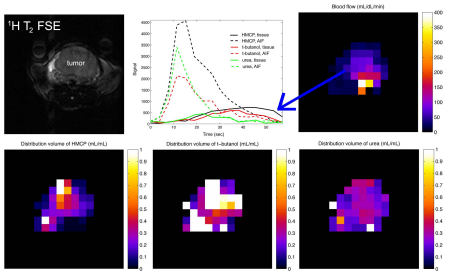


Fig 3- Axial tri-polarized images of rat brain (color) overlaid on T_2 images (gray). Images are remarkable for showing that t-butanol rapidly crosses the blood brain barrier, unlike urea & HMCP.

Table 1 / Fig. 4- Estimation of absolute blood flows in prostate tumors of 3 TRAMP mice based on dynamic tri-polarized perfusion data.

F (mL/dL/min)	78	65	49
$\mathbf{V_T}$ HMCP	0.22	0.03	0.20
$\mathbf{V_T}$ t-butanol	0.53	0.11	0.31
$\mathbf{V_T}$ urea	0.21	0.07	0.13



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