Preclinical & Clinical Applications of Hyperpolarized Contrast Agents

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The development of technology that uses Dynamic Nuclear Polarization to generate hyperpolarized ^{13}C agents and provides a dissolution process for preparing the agent in order to inject into living subjects has opened the door to pre-clinical and clinical applications. The prototype polarizer designed in Malmo, Sweden has been shown to provide a >10,000 fold signal enhancement for detecting ^{13}C probes and to have the potential for monitoring fluxes through multiple biochemical pathways such as glycolysis, the citric acid cycle and fatty acid synthesis. Preliminary studies performed in normal organs and tumors have confirmed that ^{13}C-1 labeled pyruvate is delivered to tissues and converted to alanine, lactate and bicarbonate with a spatial distribution and time course that varies according to the tissue of interest.

The methodology used for in vivo studies is based on polarizing nuclear spins in an amorphous solid state at ~1^{o}K through coupling of the nuclear spins with unpaired electrons that are added to the sample via an organic free radical. Polarization from the electrons is transferred to the nuclear spins using microwave irradiation at the appropriate frequency. Bringing the cold, polarized sample into solution while preserving its nuclear polarization requires an effective dissolution process. Both the prototype system developed in Malmo and the Hypersense polarizer developed by Oxford Instruments can provide a polarization of 10-20%. The hyperpolarized liquid sample may then be used for in vivo imaging or spectroscopy given appropriate rapid data acquisition sequences.

The choice of hyperpolarized substrate is based both on metabolic and MR properties. A long T_1 is required to maintain the polarization until the time of in vivo imaging. The T_1 of ^{13}C in small molecules are significantly longer (> 10s), particularly when the ^{13}C is a carbonyl carbon with no nearby protons. Because the C-1 carbonyl of pyruvate has an *in vivo* T_1 of 40-70s it is a promising agent for further study. Another advantage of using ^{13}C is that unlabeled tissues produce negligible signal, so that the hyperpolarized substrate and subsequent metabolic products provide the dominant contribution to the corresponding data. These considerations have meant that C_1 labeled pyruvate being the first agent considered for *in vivo* applications. As is indicated in a recent multi-author white paper, a large number of other agents are being evaluated in pre-clinical studies in multiple pathologies. Advantages of the technique are that it allows the acquisition of ^{13}C MRS data with very high temporal resolution (in the order of seconds) and the observation of real time, tissue specific metabolic changes.

Hyperpolarized ^{13}C pyruvate has been applied to murine models for evaluation of cardiac function and of a number of different cancers, including brain tumors, lymphoma, prostate, breast, liver and kidney cancers. In these studies dynamic non-localized ^{13}C MR spectra are typically obtained with a 2-4 second time resolution and low tip angle. These data have demonstrated the uptake and time course of the hyperpolarized ^{13}C pyruvate and its metabolic products ^{13}C-lactate, ^{13}C-alanine and ^{13}C-bicarbonate. Establishing the kinetics of these metabolic changes is critical for designing the data acquisition procedures and translating the findings into the clinic. The application of MR pulse sequences that use echo planar, spiral k-space sampling, compressed SENSING and/or parallel imaging strategies are critical for optimally using the pre-polarized signals and for obtaining dynamic spatially resolved data. Since the initial studies with pyruvate a number of other agents have been examined, including biocarbonate, urea, fructose, fumarate and ethyl pyruvate. These studies have demonstrated the feasibility of using the technology to provide non-invasive biomarkers for characterizing disease processes and serially monitoring response to therapy.

The feasibility of using the methodology in human subjects was demonstrated in initial studies of pyruavte metabolism in dog prostate. In this case a volume ^{13}C transmit coil and endorectal ^{13}C /^{1}H receive coil that were were used. The levels of polarization were reproducible with a mean of 19.7% and a standard deviation of 1.4%. The average arrival time for the pyruvate was 26s (range 24 to 30s) and the peak of pyruvate intensity was at 43s (range 39 to 48s). The signal-to-noise ratio for MRSI data varied from 154:1 to 361:1 for pyruvate and 25:1 to 67:1 for lactate. These studies provided strong evidence for the feasibility of translating the hyperpolarized ^{13}C technology to patients. Translating the methodology into a clinical tool for evaluation of cancer or other diseases has required a numnber of modifications of the process. The start point was the availability of appropriate ^{13}C tracers and the polarizer equipment that can generate a sterile hyperpolarized sample, which could be delivered to the subject with a delay time of the order of 15-20s. For pre-clinical studies, the trityl radical was not removed from the sample preparation. Although there were no adverse events of either pyruvate or trityl in any of animals studied, the trityl must be removed from the solution for human studies. The prototype system at UCSF, which generates human doses of sterile pyruvate is sited in a clean room environment adjacent to a 3T whole body MR scanner. The first patients studied with agents from this system have been men with biopsy proven prostate cancer who are on a regimen of watchful waiting. The first two cohorts of patients in the dose escalation phase of the study have shown excellent quality data with no adverse events. While this initial focus was on prostate cancer, the methods being developed are expected to have general applicability to a wide variety of cancers and to other pathologies. The potential and applicability of this unprecedented new metabolic imaging modality are still being investigated, but all signs are that it will be a promising technology for future study. The following is a list of relevant litrature that reflects the scope of studies that are underway.

Literature of Interest

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