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Hyperpolarized MR – What's up Doc?

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ABSTRACT

Hyperpolarized MR by dissolution Dynamic Nuclear Polarization (dDNP) appeared on the scene in 2003. Since then, it has been translated to the clinic and several sites are now conducting human studies. This has happened at record pace despite all its complexities. The method has reached a pivotal point, and the coming years will be critical in realizing its full potential. Though the field has been characterized by strong collaboration between academia, government and industry, the key message of this perspective paper is that accelerated consensus building is of the essence in fulfilling the original vision for the method and ensuring widespread adoption. The challenge is to gain acceptance among clinicians based on strong indications and clear evidence. The future appears bright; initial clinical data looks promising and the scope for improvement is significant.

1. Introduction

Hyperpolarized MR [1,2] has made tremendous progress over the past decade due to the persistent and unselfish efforts of so many people. The progress is clearly a testimony to the stamina of all these people. The method has progressed with record pace from idea [3] to first in man [4]. However, in recent years, the questions are often asked: "So what, nothing seems to happen. We still do not know what it can do for us after all these years. It is simply too hard; complicated and costly. As if, MR was not already sufficiently complicated!" Throw into the mix several additional high tech ingredients, such as spectroscopic imaging of low gamma nuclei and sophisticated polarizer technology and pharmacy, and you are bound for trouble. Well, it is hard, but I will argue that significant progress has been made, and it is all worth it! Not only is it worth it, but we could also be at the risk of emptying the baby with the bathwater, if patience or focus is lost. The vision is evident; almost all disease leads to changes in metabolism long before anatomical or functional changes are observed. Likewise, treatment of disease requires that normal cell function is restored or that malignant cells are killed. Thus, biomarkers of metabolism are expected to be sensitive and specific to disease stage and response to treatment. MR has some inherent advantages in imaging metabolism through it spectroscopic nature (chemical shift dispersions), being quantitative in principle, non-invasiveness and with no use of ionizing radiation. Hyperpolarized MR builds on this foundation, but tackles the fundamental issue of sensitivity in magnetic resonance. Despite the limited lifetime of hyperpolarization, several bioprobes with low toxicity, high cellular uptake and fast metabolism have been identified. Actually, the fast imaging of hyperpolarized metabolic contrast agent can be easily integrated into a clinical MR protocol by addition of a few minutes.

Since the first human study with hyperpolarized ^{13}C-pyruvate in men with prostate cancer [4] at UCSF in 2013, approx. eight additional groups have received approval for human studies with the SPINlab polarizer [5]. Initial clinical experience has been published by several of these groups [4,6–11]. Now that the feasibility of hyperpolarized MR has been established, the community has to come together to decide for studies with well-defined clinical endpoints that will have impact on patient management. At this point in time, the most important concern for hyperpolarized MR in the clinical translation, is demonstrating clinical value at multiple sites for common patient populations, addressing unmet medical needs. Continued public and commercial funding will most probably rely critically on demonstrating clinical value in the short term. At this point in time, 25 clinical trials are registered on clinicaltrials.gov for hyperpolarized pyruvate. Most are within cancer; e.g. prostate, breast, renal and lymphoma:

1. Characterization of prostate cancer (prediction of Gleason score, 30 patients, Sunnybrook).
2. Reproducibility in malignant solid tumors, specifically sarcoma, prostate, breast, brain or metastatic cancer (84 patients, MSKCC).

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3. Response to androgen signaling inhibitors in castration-resistant prostate cancer (75 patients, UCSF).
4. Optimization of imaging sequences in patients with prostate cancer on active surveillance (60 patients, UCSF).
5. Diagnosing glioma in patients with brain tumors (13 patients, MD Anderson)
6. Safety and toxicity in children with brain tumors (phase 1 study with 9 patients, UCSF)
7. Metabolic Imaging of the Heart in healthy subjects and those with hypertension or hypertrophy (112 subjects, Sunnybrook)
8. Feasibility of imaging breast cancer patients receiving neoadjuvant chemotherapy (phase 1 study 13 patients, Sunnybrook)
9. Imaging of bone-metastatic prostate cancer (10 subjects, Sunnybrook)
10. Correlation of pyruvate-to-lactate with histological grade (50 patients, UCSF)
11. Treatment response in patients with locally advanced cervical cancer (10 patients, Sunnybrook)
12. Feasibility in patients with prostate cancer (MD Anderson, 10 patients)
13. Imaging and treatment response in patients Glioma (80 patients, UCSF)
14. Treatment response in patients with solid tumors (prostate cancer patients with liver metastasis) (40 patients, UCSF)
15. Detection of brain tumors (10 patients, Stanford)
16. Stratification of patients with intracranial metastasis treated with radiotherapy (121 patients, Sunnybrook)
17. Patients with brain tumors (16 patients, UTSW)
18. Cardiotoxicity of chemotherapy (110 patients, UTSW)
19. Brain metabolism in healthy subjects (28 subjects, UTSW)
20. Patients with musculoskeletal sarcoma (20 patients, UTSW)
21. Effect of Fatty Liver on pyruvate metabolism (16 patients, UTSW)
22. Observational study in patients with high grade ovarian cancer (40 patients, Cambridge)
23. Patients with traumatic brain injury (16 patients, UTSW)
24. Changes in heart metabolism in patients with hypertrophic cardiomyopathy (10 patients, UTSW)
25. To assess response to treatment or aggressiveness (UCL).

Each of these clinical endpoints could be the answer to the eminent question: what can hyperpolarized MR deliver in terms of improved patient management. Is the benefit to the patient of such character that it can lead to reimbursement, or that clinicians will refer for the test? To be successful, a company has to invest in full clinical development and registration for a reimbursable indication. I believe that there will be several indications that meet these requirements. Based on the knowledge that we have today, in my opinion, an excellent proposal would be monitoring of therapy response in patients with breast cancer. Preliminary data was presented at the recent ISMRM from University of Cambridge, demonstrating response to treatment after first treatment with neoadjuvant therapy in a patient with grade 3 triple negative breast cancer. Breast cancer is the most common cancer in women. The prognosis is good, with many available treatment options. A test that could differentiate responders from non-responders already after the first treatment would improve the prognosis and quality of life as well as save significant healthcare costs. Aggressive breast cancer is highly glycolytic, and a decrease in the lactate signal would reveal responders. Clinical practice in breast cancer is to offer the patient neoadjuvant chemotherapy before surgery possibly followed by adjuvant therapy. Today, response to therapy is detected as a decrease in tumor size and lesions, after typically 12 treatments over three months. This patient group would strongly benefit from having predictive diagnostic imaging without radiation exposure.

Making the clinical vision a reality will require collaboration and coordination within the scientific community. There are many examples of promising technologies and methods that have failed due to inconsistent and inconclusive data, e.g. due to bad study design, technical variability or non-conformance. It is therefore critical for the success of hyperpolarized MR that data acquisition and analysis standards are established in a similar manner as recently published in a consensus paper on brain ^{1}H MRS [12]. The community has to come together for this together with the major MR vendors. Tremendous pulse sequence development has taken place and now allows 3D spatial imaging over large field-of-view with high temporal resolution of several metabolites by use of EPI [13,14] or spiral trajectories [15,16] in combination with IDEAL or spectral-spatial pulses and parallel imaging. A standardized, shareable data acquisition and analysis platform, independent of scanner would facilitate this objective, e.g. through third party vendor independent platforms such as RTHawk (Heartvista, CA, US) as demonstrated by Tang et al. [17]. Data analysis also needs to be standardized, and robust, quantitative measures defined such as e.g. k_{PL} maps overlaid on anatomical ^{1}H images [18,19]. Clinicians demand simple, easily interpretable criteria for assessing e.g. aggressiveness of cancer or response to treatment.

The pharmacy of hyperpolarized MR has presented significant technical challenges. The polarization process has to ensure that the product is safe and efficacious. The approach that has been pursued is to use a sterile, single-use, plastic cassette (the fluid path) with the pharmaceutical ingredients being filled in a clean room. The fluid path is exposed to rather extreme conditions. In the process, parts of the fluid path are cooled to 1 K superfluid helium while other parts are heated to 130 °C under a pressure of 16 bar. In the dissolution process, the fluid path is under severe thermal and mechanical stress. In principle, the process is simple, but cost, complexity and engineering trade-offs are delicate. Other concepts could be imagined that would significantly simplify the process and reduce costs. A clean-in-place or sterile-in-place process would allow the fluid path to be broken into smaller units, e.g. the pyruvic acid in small capsules and solvents drawn from bulk: a "Spinpresso" concept. The major part of the fluid path would be integral to the polarizer and re-used after sanitization. Other parts would be single-use. In essence, hyperpolarized MR is not inherently expensive. Stable isotope enrichment has added costs, but the isotopes are abundant. Infrastructure investments (e.g. polarizer and MR scanner upgrades) can be amortized over thousands of patients. It seems reasonable that hyperpolarized MR would be cost-effective for the right indications and would have similar costs as other molecular imaging contrast agents.

Further improvement of the sensitivity and image quality of hyperpolarized MR can be achieved through improved coil designs. The lower detection frequency of ^{13}C, means that electronic noise may easily dominate the receiver. In particular for array coils with small element size and high channel count [20,21], or nuclei with even lower gyromagnetic ratio, such as ^{15}N. A strategy to reduce noise in these situations, could be through cryogenic coil and amplifier technology [22,23]. The lower ^{13}C Larmor frequency has advantages, such as higher element decoupling and more predictable sensitivity profiles as priors in the image reconstruction. Coil arrays enable parallel imaging to accelerate image acquisition with little penalty in signal-to-noise ratio [24]. The availability of full-bore, homogeneous ^{13}C transmit coils integrated with the ^{1}H body coil (dual-tuned), provides homogenous transmit fields that are easily calibrated prior to patient scans. Further hardware improvements that may provide benefit in many scan situations are higher order shimming and ^{1}H decoupling.

Polarizer technology and methods have matured significantly [5,25–27] forecasting that infrastructure costs and workflow will become acceptable. High liquid state polarization, approx. 70%, has been demonstrated for pyruvate with trityl [25]. Further signal gains will come from faster transfer from polarizer to patient. Currently, quality control release procedures have several manual steps and redundancy. Many of the published studies report 60–90 s delay from dissolution to injection, which in principle could be reduced to approx. 30 s.

The basic science within hyperpolarization is still flourishing. I see great opportunities for liberating hyperpolarization from the MR scanner by transportable polarized solids [28,29], alternative ways for hyperpolarization like PHIP-SAH (competition is good) [30], cross-polarization for low-gamma, dilute spins to accelerate and enhance nuclear polarization [31,32], bullet-DNP for fast transfer and minimal dilution [33], many new in vivo substrates [2,34] and polarizing agents with optimized properties for specific substrates and applications [35–38]. A subset of all the exciting new ideas that continuously appear in the field.

I am clearly very optimistic about the future of hyperpolarized MR. The challenge is not to identify the medical killer application; but to pick one! In this opinion article, I have tried to lay out some of the challenges and opportunities that we face with the method, and I have made specific suggestions for where the field needs to focus attention. Most importantly, the field has to come together to establish consensus on methods and join forces in multi-center trials to build a foundation for full clinical development of hyperpolarized MR. If this does not happen, hyperpolarization risks remaining an exotica of magnetic resonance.

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Disclosure

The author is an employee of GE Healthcare and the owner of the company Polarize (www.polarize.dk).

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