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Hyperpolarized MRI – An Update and Future Perspectives

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In recent years, hyperpolarized ^{13}C magnetic resonance spectroscopic (MRS) imaging has emerged as a complementary metabolic imaging approach. Hyperpolarization via dissolution dynamic nuclear polarization is a technique that enhances the MR signal of ^{13}C-enriched molecules by a factor of $> 10^4$, enabling detection downstream metabolites in a variety of intracellular metabolic pathways. The aim of the present review is to provide the reader with an update on hyperpolarized ^{13}C MRS imaging and to assess the future clinical potential of the technology. Several carbon-based probes have been used in hyperpolarized studies. However, the first and most widely used ^{13}C-probe in clinical studies is [1-^{13}C]pyruvate. In this probe, the enrichment of ^{13}C is performed at the first carbon position as the only modification. Hyperpolarized [1-^{13}C]pyruvate MRS imaging can detect intracellular production of [1-^{13}C] lactate and ^{13}C-bicarbonate non-invasively and in real time without the use of ionizing radiation. Thus, by probing the balance between oxidative and glycolytic metabolism, hyperpolarized [1-^{13}C]pyruvate MRS imaging can image the Warburg effect in malignant tumors and detect the hallmarks of ischemia or viability in the myocardium. An increasing number of clinical studies have demonstrated that clinical hyperpolarized ^{13}C MRS imaging is not only possible, but also it provides metabolic information that was previously inaccessible by non-invasive techniques. Although the technology is still in its infancy and several technical improvements are warranted, it is of paramount importance that nuclear medicine physicians gain knowledge of the possibilities and pitfalls of the technique. Hyperpolarized ^{13}C MRS imaging may become an integrated feature in combined metabolic imaging of the future.
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Introduction

In recent years, metabolic imaging has been increasingly used to guide treatment decisions in a variety of clinical specialties such as oncology, neurology, cardiology, and rheumatology.[1] The application of ^{18}F-fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) is the most common and serves as the workhorse of clinical metabolic imaging. FDG-PET can measure glucose uptake in the tissue. However, it cannot detect downstream metabolism,[2] leaving FDG-PET blind to cases where of disturbed intracellular glucose metabolism might guide treatment decisions.[3] Magnetic resonance spectroscopy (MRS) is a well-known, non-invasive technology with the ability to obtain downstream metabolic information.[4] However, the clinical application of MRS has been limited by an intrinsically low sensitivity as compared with other analytical methods.[5] MRS is based on the interaction of the magnetic moment of nuclei of various atoms within a magnetic field. Only certain nuclei such as ^{1}H, ^{31}P, ^{13}C and ^{15}N have a magnetic moment.[6] In metabolic imaging of carbon-rich molecules such as glucose and its breakdown products, the stable ^{13}C isotope is of particular interest. However, as the natural abundance of ^{13}C is only 1.1 % of all carbon, the MR signal is inherently low and its use in metabolic

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imaging is limited[5]. Hyperpolarized ^{13}C MRS imaging (MRSI) is an emerging method, with the ability to transiently enhance the MR signal of ^{13}C-enriched molecules by > 10.000 times.[5] One of the most widely studied ^{13}C-probes in hyperpolarized MRSI is ^{13}C enriched pyruvate[1]. Pyruvate is the end-product of intracellular glycolysis. Depending on the prevailing metabolic state, pyruvate is either metabolized into lactate or acetyl-CoA with CO_2/HCO_3^- being cleaved of before acetyl-CoA enters the Krebs cycle in the mitochondria[7] (Fig. 1B). Thus, hyperpolarized ^{13}C pyruvate MRSI can detect important metabolic changes, such as the increased lactate production in malignant tumors (the Warburg effect)[8,9] or lactate production in regions of myocardial ischemia and bicarbonate production in regions of viable myocardium.[10] In this review, we will provide an overview of the current status of preclinical and clinical hyperpolarized ^{13}C MRSI and focus on the future clinical applications of this emerging metabolic imaging method.

Hyperpolarization and imaging of ^{13}C-probes

In a strong magnetic field, as in the bore of the magnetic resonance imaging (MRI) scanner, MR active nuclei such as ^{13}C behave like bar magnets and align in the same orientation as the applied magnetic field. However, nuclei will either align in the same direction (parallel) or in the opposite direction (antiparallel) to the magnetic field.[7] The net magnetic energy difference in parallel and antiparallel nuclei is the polarization level and forms the basis of the MR signal.[11] At body temperature the polarization level of ^{13}C is 0.0005 %, producing a very low MR signal.[7] One way to improve the MR signal of ^{13}C-probes is to synthetically enrich the ^{13}C label to 99% in the molecule of interest and increase the strength of the magnetic field in the MR scanner.[1] Another way is to increase the polarization level (hyperpolarization) of the ^{13}C probe, giving rise to > 10.000-fold increase in the MR signal.[5] The most widely used method for hyperpolarization of ^{13}C is dissolution dynamic nuclear polarization (dDNP).[5,9,12] The detailed physics of dDNP is beyond the scope of this review. However, simplified the dDNP method transfers the high polarization levels from electron spins of a free radical (electron paramagnetic agent, EPA) to ^{13}C labeled probes in an environment of extremely cold environment (0.8 °K) in a strong magnetic field (5 Tesla (T)), using microwave irradiation[5] (Fig. 1 A). After a polarization time determined by the magnetic properties of the system and the sample, typically 2 hours for [1-^{13}C]pyruvate at 5T, the polarization level is > 20 %, equivalent to a 10^5-fold enhancement in the MR signal

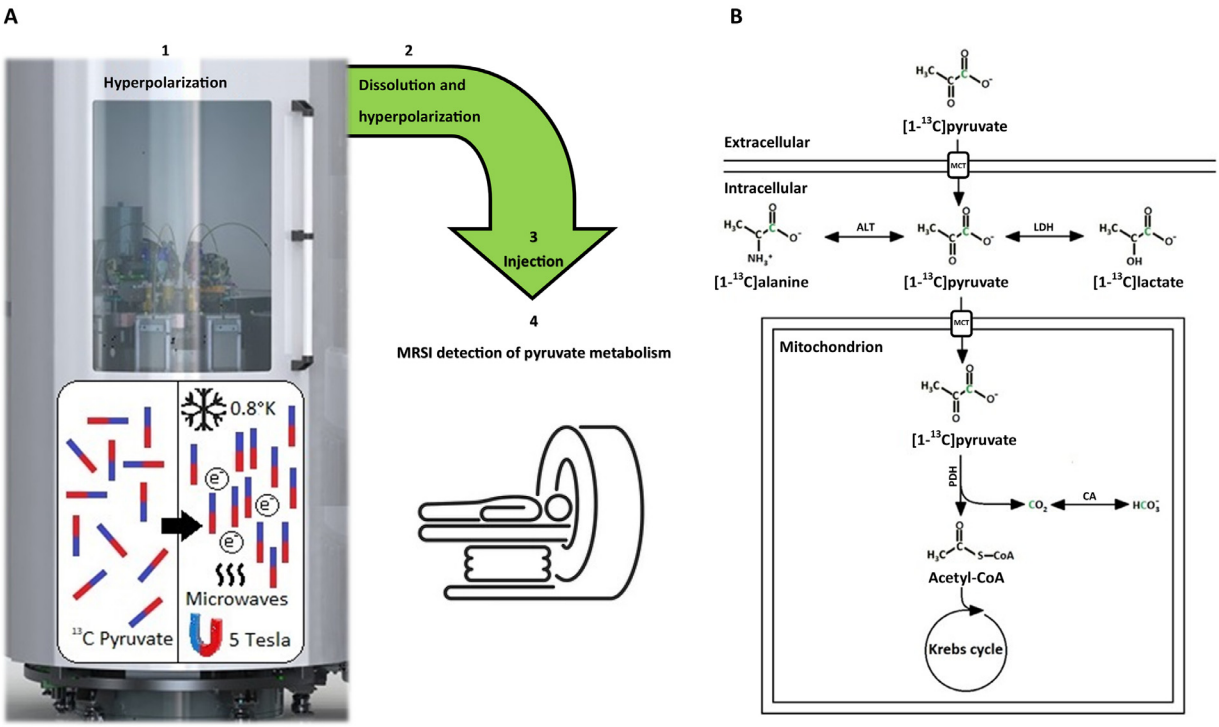

Figure 1 (A) Illustration of the dissolution dynamic nuclear polarization process in the SPINlab. First (1) up to four samples of ^{13}C-pyruvate are placed in the SPINlab and the combination of a free radical, low temperature (0.8 °K), microwave irradiation and a magnetic field of 5 T results in hyperpolarization of the ^{13}C nuclei. Second (2), the ^{13}C-pyruvate is dissoluted and quality control module ensures that temperature, pH, concentration and polarization level are acceptable for (3) injection. Fourth (4), immediately after injection into the patient, imaging starts with fast MR sequences. Spectra and images of the pyruvate metabolism are acquired. (B) Overview of pyruvate metabolism. The green C marks the hyperpolarized ^{13}C enrichment in the first position of [1-^{13}C]pyruvate and can be followed downstream. ALT = Alanine aminotransferase, CA = Carbonic anhydrase, LDH = Lactate dehydrogenase, MCT = Monocarboxylate transporter, PDH = Pyruvate dehydrogenase.

Table 1 Overview of selected ^{13}C probes and their target. LDH = lactate dehydrogenase, ALT = alanine aminotransferase, PDH = pyruvate dehydrogenase. * = [^{13}C]urea is currently used in a clinical study (clinicaltrials.gov (NCT02526368)), but to date only preclinical studies have been published. (Adapted from Wang et al.[1])

Probe	Clinical or preclinical	Metabolic pathway or physiologic process	Disease
[1-^{13}C]pyruvate	Both	Glycolysis, LDH, ALT and PDH	Cancer, ischemia, cardiac metabolism, inflammation
[2-^{13}C]pyruvate	Both	Krebs cycle	Cancer, cardiac metabolism
[1-^{13}C]bicarbonate	Preclinical	pH	Cancer, ischemia
[1,4-$^{13}C_2$]fumarate	Preclinical	Cellular necrosis	Cancer, ischemia
[1-^{13}C]acetate	Preclinical	Krebs cycle, fatty acid oxidation	Ischemia, cardiac metabolism
[2-^{13}C]dihydroxyacetone	Preclinical	Gluconeogenesis	Diabetes
[1,3-$^{13}C_2$]acetoacetate	Preclinical	Redox	Cancer, ischemia, diabetes
[^{13}C]urea	Both*	Perfusion	Cancer, ischemia, vascular disease

when imaging is performed in 3 T MR scanner.[5,12,13] The sample is then rapidly dissolved and must pass a quick quality assessment (polarization level, pH, pyruvate concentration, EPA concentration and temperature) before being injected into the patient. The enhanced MR signal decays rapidly (1-2 minutes) and imaging must be performed immediately to acquire high signal-to-noise metabolic data.[4] The so called SPINlab (GE Healthcare) has automated all these processes and is the only commercially available clinical hyperpolarizer. With the SPINlab integrated in the MR suite, it is feasible to use hyperpolarized ^{13}C-probes in a clinical setting.[12] The acquisition of ^{13}C data requires an MRI scanner with hardware enabling the excitation and detection of the ^{13}C frequency.[3] Further, optimized MR sequences are used to acquire the ^{13}C-signal before it decays. This allows for encoding of 5D data (3 spatial + 1 spectral + 1 temporal). Spectral encoding is necessary to image both substrates and metabolic products and temporal encoding makes it possible to measure metabolism kinetics including conversion rate constants of pyruvate to lactate (k_{PL}) and pyruvate to bicarbonate (k_{PB}).[14,15] Hyperpolarized ^{13}C data acquisition is usually complete within 2 minutes after injection of the ^{13}C-probe. Afterwards, ^{13}C-data can be overlaid an anatomical ^{1}H-MRI image of the region of interest (eg, heart or brain) to visualize anatomical differences in metabolism.

^{13}C Probes

Currently, there are numerous ^{13}C-probes, mainly endogenous biomolecules with ^{13}C enrichment as the only modification.[16] To image intracellular metabolic processes, probes are injected at supraphysiologic doses and it is required that the probes has a sufficiently rapid transport over the cell membrane and a fast metabolism in order to allow acquisition of metabolic data during the short time span of a hyperpolarized MRI study[1]. Presently, [1-^{13}C]pyruvate with ^{13}C replacing the first carbon atom is the most studied probe in clinical hyperpolarized MRSI studies. Also [2-^{13}C]pyruvate with ^{13}C in the second position is approved for human application and have been used in preclinical studies to detect mitochondrial metabolism as the ^{13}C-label follows acetyl-CoA into the Krebs cycle.[1] As an example of a metabolically inactive probe, Lau et al. has demonstrated that [^{13}C]urea can be co-polarized with [1-^{13}C]pyruvate to simultaneously measure myocardial perfusion and pyruvate metabolism in the rat heart.[17] According to clinicaltrials.gov, a human phase-1 study using ^{13}C and $^{15}N_2$ urea is currently ungoing (clinicaltrials.gov (NCT02526368)). Additionally, several other probes (Table 1) are being reviewed for clinical use.[1,4] An example is [1,4-$^{13}C_2$]fumarate, used in preclinical studies to measure malate production in areas of myocardial necrosis.[18,19]

Hyperpolarized [1-^{13}C]pyruvate MRS in clinical studies

Pyruvate is a key metabolite in human metabolism. Pyruvate is the end-product of glycolysis, and it serves as fuel for cellular ATP production.[20] In the cytosol, pyruvate is either reduced to lactate, by the lactate dehydrogenase (LDH), or transaminated to alanine, by the alanine aminotransferase (ALT). However, most pyruvate is transported into the mitochondria by the monocarboxylate transport carrier (MCT) and oxidized by pyruvate dehydrogenase (PDH) to CO_2 and Acetyl-CoA, entering the Krebs cycle to ultimately generate ATP by oxidative phosphorylation[7,20] (Fig. 1 B). Changes in pyruvate metabolism is a key element in major diseases such as cancer, heart failure, and neurodegeneration.[20–22] Hyperpolarized [1-^{13}C]pyruvate MRS can non-invasively detect the essential enzymatic steps in pyruvate metabolism in vivo and in real-time.[3,7,12] The MRI inherent chemical shift effect makes it possible to differentiate [1-^{3}C]pyruvate from its downstream metabolic products within seconds after injection. Thus, dynamic, real-time accumulation of [1-^{13}C]lactate is detected when LDH reduces [1-^{3}C]pyruvate to [1-^{13}C]lactate. When PDH catalyzes the oxidative decarboxylation of [1-^{13}C]pyruvate to Acetyl-CoA, ^{13}C-labelled carbon dioxide is cleaved off and rapidly equilibrates with bicarbonate.[4] The detection of [^{13}C]bicarbonate signal is used to measure the PDH activity.[23] Finally, [1-^{13}C]alanine-signal is detected as a consequence of transamination of [1-^{13}C]pyruvate to [^{13}C]alanine by ALT[4] (Fig. 2)

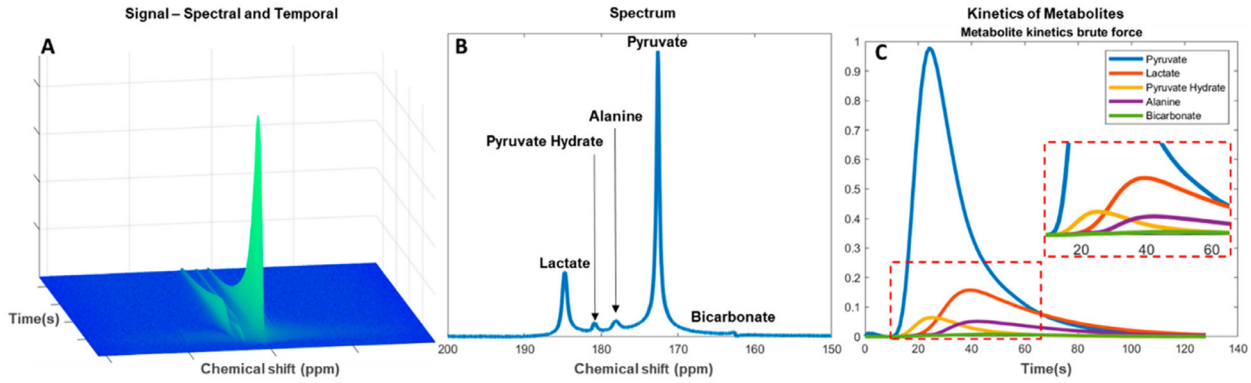

Figure 2 Analysis of hyperpolarized ^{13}C spectra from pyruvate injection. (A) Metabolite signal change in the spectral and temporal dimension after injection. (B) Total signal of downstream metabolites in a temporal summed spectrum. (C) Kinetics of the metabolites with enhanced view of smaller signal metabolites (red dashed box). Figure reprinted with permission from Vaeggemose, M.; F. Schulte, R.; Laustsen, C. Comprehensive Literature Review of Hyperpolarized Carbon-13 MRI: The Road to Clinical Application. Metabolites 2021, 11, 219. https://doi.org/10.3390/metabo11040219[4].

Cancer

In cancer cells, glycolysis is highly upregulated while oxidative phosphorylation is downregulated.[20] This metabolic switch is termed "the Warburg effect" and as a result, most malignant tumors produce large amounts of lactate[24]. Imaging of the increased conversion of [1-^{13}C]pyruvate to [1-^{13}C]lactate has been proposed as a promising method to diagnose early cancer and to detect treatment response.[8] In 2013, the first human study reported a significant increase in [1-^{13}C]lactate signal in areas of biopsy proven prostate cancer in 31 patients.[25] Several studies have reported increased conversion rates of pyruvate to lactate (k_{PL}) in both prostate cancer tumors and corresponding metastases.[26,27] Of particular interest, Aggarwal et al. found that [1-^{13}C]lactate signal declined to a minimum after only 6 weeks of anti-androgen treatment. At the same time, conventional T2-weighted MR showed only negligible change in tumor size. Decline in k_{PL} after 6 weeks corresponded to a marked clinical response after 6 months.[27] Recently, hyperpolarized [1-^{13}C]pyruvate have been used to study breast cancer. The study showed that increased [1-^{13}C]lactate signal correlated with tumor size and malignancy grade.[28] Later, a feasibility study of treatment response in breast cancer showed that hyperpolarized [1-^{13}C]pyruvate MRSI was able to identify metabolic changes after only one cycle of neoadjuvant chemotherapy.[13] Another area of research in clinical hyperpolarized MRSI has been malignancies in the central nervous system (CNS). Studies have demonstrated that hyperpolarized [1-^{13}C]pyruvate MRSI can detect increased [1-^{13}C]lactate signal in CNS tumors such as glioma and glioblastoma.[29,30] Recently, Tang et al. published a study on eleven patients with renal tumors. The study showed good reproducibility of metabolite measurements and in addition, the metabolic data indicated a trend toward differentiating low-grade and high-grade clear cell renal cell carcinoma.[31] In conclusion, initial studies have demonstrated that hyperpolarized [1-^{13}C]pyruvate MRSI provide unique metabolic information in various forms of cancer diseases. The method may complement the information gained from FDG-PET. Especially, hyperpolarized [1-^{13}C]pyruvate MRSI may be of use in detecting early treatment response and thus, allow early adaptation of therapy in non-responders. Since the initial UCSF prostate cancer study in 2013, clinical studies have been small in sample sizes making direct conclusion troublesome, nevertheless, several clinical trials are in the pipeline according to clinical.trials.org and EudraCT.[1,4]

Heart disease

Metabolic alterations are increasingly recognized as a hallmark of both heart failure (HF) and ischemic heart disease.[32] To generate energy for contractile activity, the healthy heart primarily relies on oxidation of fatty acids and to a lesser extent oxidative phosphorylation of carbohydrates.[22] In HF, it is believed that cardiomyocytes switch to increased glucose metabolism. However, animal studies indicate that although glycolysis is enhanced in HF, oxidative phosphorylation is depressed due to impaired flux through PDH.[22] As a result, a lack of energy for contractile activity may be essential in the development of HF.[33] Similarly, in myocardial ischemia, compromised coronary blood flow and subsequent lack of oxygen supply drives a metabolic switch to increased anaerobic glycolysis and hence lactate production in order to maintain contractility.[32] Currently, FDG-PET is the only clinically available tool to asses myocardial metabolism by quantifying glucose uptake.[2] However, its continued downstream fate metabolism is not detected. Therefore, hyperpolarized [1-^{13}C]pyruvate MRSI has been proposed as a promising method to directly detect myocardial ischemia and define viable myocardium as well as to identify metabolic precursors to heart failure in populations at risk.[7] In 2016, the first human [1-^{13}C]pyruvate MRSI study reported detection of [^{13}C]bicarbonate signal in the left ventricular (LV) myocardium in the healthy human heart.[34] In 2020, a study compared cardiac metabolism in healthy controls and patients with type II diabetes (T2D).[35] Interestingly, this study found

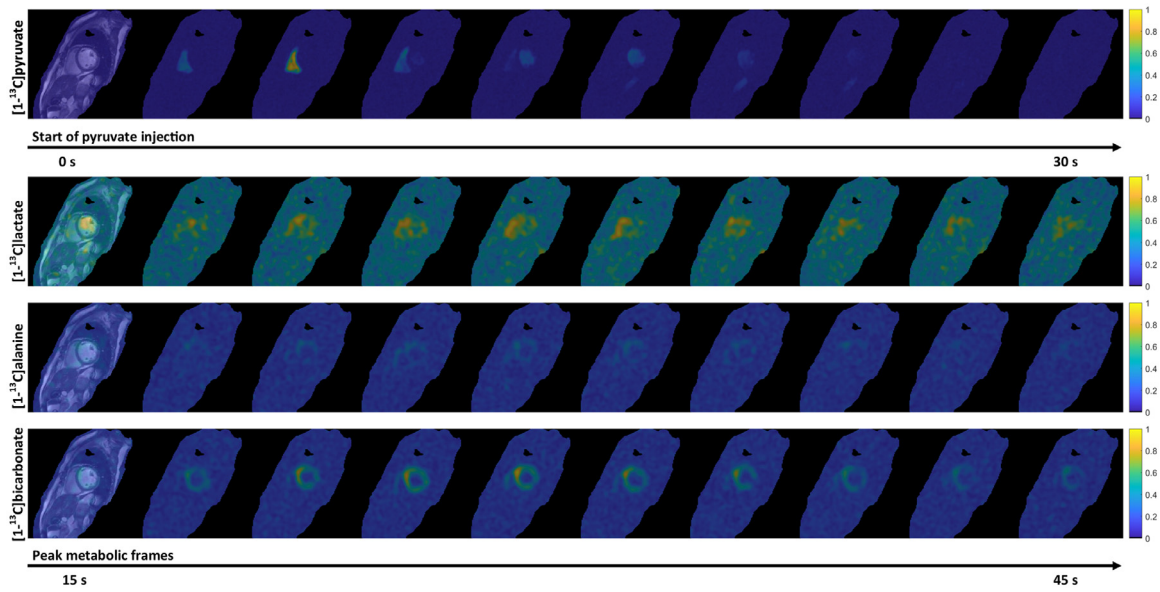

Figure 3 An example of a patient with chronic heart failure and left ventricular ejection fraction of 30%. Images shows temporal dynamics of pyruvate, lactate, alanine, and bicarbonate in a single slice at the mid left ventricular level. The left image shows the ^{1}H MRI image for anatomical reference. The right-side color scale (0-1) shows the relative signal from each metabolite. Subsequently, the left ventricular myocardium can be divided into subsegments and analyses of e.g., metabolite ratios or k_{PL} and k_{PB} can be done to assess regional differences in myocardial metabolism. (Data from own experiments at the MR-Research Centre, Aarhus University Hospital).

impaired flux through PDH of the myocardium in patients with T2D, even though both patients and healthy controls had normal left ventricular ejection fraction. In 2021, the first experience in patients with transmural myocardial infarction was reported.[36] In nonviable areas with transmural infarction, [^{13}C]bicarbonate signal was absent as an indication of reduced PDH activity. Although clinical cardiovascular studies have been small in numbers, results are encouraging and demonstrate the vast potential of hyperpolarized imaging in cardiovascular disease (Fig. 3).

Central nervous system

Cerebral metabolism is deranged in numerous pathologies of the central nervous system, including ischemia, inflammation (multiple sclerosis), infection and, as previously mentioned, cancer.[37] In 2019, a small study (n = 4) on metabolism in the healthy human brain demonstrated that in vivo imaging of cerebral [1-^{13}C]pyruvate metabolism was feasible in the presence of an intact blood-brain barrier in healthy subjects.[38] These results were confirmed in a larger study (n = 14) in 2020, showing a consistent, region specific lactate topography across subjects of varying age.[39] Recently, a clinical study of eleven patients with intracranial metastases demonstrated that hyperpolarized [1-^{13}C]pyruvate MRSI could predict patients at risk of treatment failure following stereotactic radiosurgery.[40] Autry et al. have reported initial results from six pediatric patients with CNS malignancy, confirming that the method is feasible, even in pediatric patients.[41] These encouraging results holds promise for a substantial potential of human hyperpolarized [1-^{13}C]pyruvate MRSI of CNS pathologies in the future. At present, several clinical studies on [1-^{13}C] pyruvate metabolism in the brain is ongoing, including a study on patients with amyotrophic lateral sclerosis and a study on patients with persistent post covid-19 symptoms (EudraCT # 2020-000352-36 and 2021-001031-72).

Technical requirements and advances in hyperpolarized ^{13}C MRI

Preclinical and recent clinical studies have elucidated a vast potential for hyperpolarized ^{13}C metabolic imaging. However, despite several technical advances and standardization of techniques, the emerging method is not yet implemented in clinical metabolic imaging. Hyperpolarized ^{13}C MRSI remains costly and technically demanding. In the following section, we will summarize some of the recent technical advances and address additional opportunities.

Hyperpolarization

Hyperpolarized ^{13}C MRSI has certainly come a long way since 2003, when Ardenkjaer-Larsen et al. introduced the d-DNP polarizer.[5] With the development of the commercially available, clinical 5T SPINlab (GE Healthcare), several technical steps have been automated.[42] The SPINlab can hyperpolarize four samples at a time and quality assessment is integrated into the system, making it simpler to operate. Currently, the SPINlab is installed at 24 sites around the world. The ^{13}C probes, the EPA, and the buffers for dissolution are compounded in a commercially available pharmacy kit

following Good Manufacturing Practice. At present, only [1-^{13}C]pyruvate, [2-^{13}C]pyruvate an [^{13}C]urea are approved for human use, but it seems likely that several other probes will soon be available for clinical studies.[3] Co-polarization or repeated administration of different probes will allow simultaneous or consecutive clinical investigation of several metabolic pathways and perfusion in a near future.[17,43] A major obstacle in the dissemination of hyperpolarized MRSI has been the fact that hyperpolarization is both a time consuming and a technically challenging process, requiring specially trained personnel with expertise in producing hyperpolarized probes, monitoring their quality, and assuring patient safety and regulatory compliance.[3] Further, interpretation of data requires trained staff members and physicians. To aid a wider clinical implementation, there is a need for additional technical advances, leading to further automation of the technique and higher and faster polarizations with an improved cost-effectiveness.[3] In this regard, it is essential to mention parahydrogen-induced polarization (PHIP). This is a possible future alternative to dDNP. PHIP is still experimental, but the method has the potential to become more cost-effective than dDNP and PHIP can achieve polarization faster than dDNP.[4] Additionally, multicenter trials are necessary to assure the ability of multiple sites to produce uniformly high-quality hyperpolarized probes and to assure that imaging data are acquired and analyzed in a uniform and reproducible fashion. Thus, multicenter trials are needed to validate the findings from single-center trials before hyperpolarized ^{13}C probes can be approved as clinical imaging agents.[3]

Data acquisition and imaging hardware

The ^{13}C-probes resonates at a different range of frequencies than standard ^{1}H imaging. So, in order to acquire metabolic data, the hardware must allow excitation and detection of the hyperpolarized signals at the ^{13}C frequency.[3] Fortunately, all major suppliers of MR scanners offer such hardware. However, in order to enhance patient comfort and improve the workflow, development of dual-tuned or nested receive arrays that would allow high-quality ^{1}H imaging alongside sensitive ^{13}C acquisition, without repositioning or replacing coils, is essential.[1,3,4] Further, it is recommended to use a 3 T MRI scanner as the spectral separation of pyruvate and its metabolites is doubled when field strength is increased from 1.5 T to 3 T, even though the larger field strength shortens the relaxation time of [1-^{13}C]pyruvate[1]. Besides dedicated hardware, hyperpolarized MRSI studies require specialized sequences due to the fast metabolism and rapid, non-renewable decay of the signal.[12] Generally, trade-offs must be made between the acquired information of the five dimensions of the experiment (three spatial, time, and spectral).[15] The initial studies primarily acquired spectra or a grid of spectra, so called magnetic resonance spectroscopy imaging, gaining good spectral resolution but without dynamic information, yielding this approach vulnerable to probe delivery and acquisition timing differences. To enable acquisition of the entire temporal dynamics, more recent studies have been using fast imaging approaches, sacrificing the spectral dimension. This requires sufficient spectral separation, prior knowledge of the resonances of interest, and correct calibration of the center frequency when planning the scan; for [1-^{13}C]pyruvate, these are relatively easily fulfilled. In this type of experiment, the resonances of pyruvate and metabolites are selectively excited in a gradient echo type sequence followed by a fast readout. This further allows excitation of pyruvate and metabolites with different flip angles, using magnetization in a more optimal way. Our current recommendation is to use spectral-spatial metabolite selective excitation with low flip angles on pyruvate and higher on the metabolites. The readout should preferentially be a spiral or alternatively an echo-planar imaging readout. The entire temporal dynamics should be acquired with temporal resolution around 1 to 3 seconds. Spatial resolution depends on the organ of interest and the hardware available, but around 15 mm isotropic is a good starting point. This approach further allows acquiring pyruvate and the metabolites at different spatial and temporal resolutions, taking advantage of the high pyruvate signal available.[14,44] Currently, the potential advantages of accelerated acquisitions, balanced steady-state free precession type sequences, and 3D imaging are under investigation.[45,46] For now, the recommended framework allows robust imaging across a variety of organs and setups in clinical trials.

Conclusion

Hyperpolarized ^{13}C imaging offers enhanced information on metabolism to an extent that is impossible to obtain with current imaging techniques. Further, the method enables metabolic imaging without using ionizing radiation or nephrotoxic contrast. The recent introduction of combined PET and MR in clinical imaging leads to the obvious question: can ^{13}C MRSI become an integrated feature in combined metabolic imaging of a near future? There is no doubt that the additional information gained from a combination of PET and hyperpolarized ^{13}C imaging would be a powerful tool to investigate essential metabolic derangements in a variety of major diseases such as cancer and cardiovascular diseases. Improved early detection of disease, staging and treatment monitoring are possible benefits and therefore, personalized and targeted treatment becomes feasible with enhanced metabolic imaging using hyperpolarized ^{13}C MRSI.

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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