Hyperpolarized 13C Magnetic Resonance

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Hyperpolarized 13C magnetic resonance (MR) is a promising technique for the noninvasive assessment of the regional cardiac metabolism since it permits heart physiology studies in pig and mouse models.

Keywords: magnetic resonance ; radio frequency coils

1. Introduction

Cardiovascular magnetic resonance (CMR) represents a powerful tool in the noninvasive assessment of cardiac anatomy, function, and metabolism [1]. CMR applications cover a broad spectrum of clinical and research areas, such as global and regional cardiac function, myocardial perfusion, myocardial viability, tissue characterization, and proximal coronary anatomy.

Magnetic resonance spectroscopy (MRS) represents an accurate, noninvasive, non-ionizing tool for in vivo evaluation of cardiac metabolism, with applications to various nuclei (^{1}H, ^{31}P, ^{13}C) [2][3].

In particular, 13C spectroscopy can be used for an investigation of the intermediary metabolism of biomolecules in vivo [4]. ^{13}C nuclei generate a natural signal, which is very low and difficult to detect with conventional magnetic resonance (MR) scanners due to the scarce natural abundance and the low level of nuclear polarization at thermal equilibrium. The low ^{13}C signal is even more critical if the study involves a moving organ such as the heart. Recently, the development of hyperpolarization techniques for enhancing ^{13}C polarization has led to a significant nuclear magnetization increase. In particular, the hyperpolarization technology known as dissolution dynamic nuclear polarization (dDNP) enhances the polarization of ^{13}C by a factor of 100,000 [5].

However, several technological problems still limit the application of these techniques and require innovative solutions, especially when a low molar concentration of metabolites reduces the in vivo sensitivity.

Despite the use of hyperpolarized ^{13}C tracers, the design and development of both dedicated radio frequency (RF) coils and acquisition settings need to be specialized for the region of interest, and potentially for the animal of interest, to provide the optimal signal-to-noise ratio (SNR). In particular, RF coils have to guarantee a large field of view (FOV) with high magnetic field homogeneity in transmission (TX) and to achieve high SNR in reception (RX) [6]. Moreover, ^{13}C experiments require that the MR system operates at two different frequencies (multinuclear system) to provide 1H imaging and ^{13}C acquisition with the same experimental setup. Multinuclear acquisitions can be performed by using two separate RF coils or by using a single dual-tuned coil operating at two different frequencies. The choice of the most suitable coil for a given application is a necessary constraint. Recently, a quality assurance imaging protocol for ^{13}C coils based on MR spectroscopic imaging was described in the literature [7], in which different coil setups were tested and compared.

2. Hyperpolarized 13C Magnetic Resonance

Hyperpolarization increases the measured MR signal strength by many orders of magnitude, thus, overcoming the intrinsic MR sensitivity limitations [8].

Hyperpolarized ^{13}C has been investigated for imaging the metabolism in various cancers and cardiac diseases. The most common hyperpolarized ^{13}C-labeled agents include small molecules that play a central role in the major metabolic cycles in normal and diseased functions. In particular, [1-^{13}C]pyruvate is rapidly transported to the intracellular space via the monocarboxylate transporters, where it is used as a probe to track the intracellular metabolism. [1-^{13}C]pyruvate has been applied to investigate metabolic disorders, tumor response to therapy, cancer detection, cerebral dynamics and metabolism, pH, and more.

In addition to pyruvate, other hyperpolarized ^{13}C substrates have been investigated from [1,4-$^{13}C_2$]fumarate to [1,4-$^{13}C_2$]malate. Moreover, ^{13}C-bicarbonate and ^{13}C-carbon dioxide have been investigated to measure extracellular pH. Other ^{13}C-labeled substrates applied to cardiac functional or metabolic imaging include [U-^{13}C]α-ketobutyrate, [1-^{13}C]lactic acid, [1-^{13}C]acetate, ^{13}C-urea, and [1-^{13}C]butyrate [9].

The most common ^{13}C-labeled agents include small molecules that play a central role in the major metabolic cycles in normal and diseased functions. For a given metabolic pathway, the choice of metabolic substrate and the specific ^{13}C label site dictate the T1 time and the metabolic tracer's chemical shift. In turn, the T1 time influences the total acquisition time and SNR for imaging and spectroscopy. The chemical shift may further constrain acquisition parameters (e.g., echo time or RF excitation bandwidth) depending on the spectral bandwidth required to discriminate between different metabolic species.

Among the hyperpolarization techniques, currently, dDNP is the most promising from a clinical perspective [5][10]. In brief, dDNP is performed at high magnetic field (3.35 to 7 T) and extremely low temperature (≈1 K), where the high polarization of electron spins (unpaired electrons of radical molecules added to the sample at mM concentration) is transferred to nuclear spins by microwave irradiation. Rapid dissolution of the sample is subsequently performed to produce hyperpolarized solutions that can be injected for in vivo studies [11]. The ^{13}C-pyruvate is the gold-standard molecule for DNP clinical and preclinical applications due to its optimal chemo-physical properties, long T1 relaxation time, high ^{13}C concentration, as well as its key role in cell metabolism. To investigate tissue metabolism, an isotopically labeled compound (usually a ^{13}C-enriched molecule such as ^{13}C-pyruvate) is hyperpolarized and readily injected in vivo, where it participates in enzyme-mediated metabolic reactions. Using MRS, the injected compound and its metabolic products can be selectively detected in a noninvasive manner and in real time [12][13].

The hyperpolarized signal rapidly decays once the hyperpolarization process is concluded due to T1 relaxation. For the most used ^{13}C-labeled compounds, T1 is of the order of a few tens of seconds, and the MR signal decay occurs in a few minutes. Because of this rapid and irreversible decay, fast signal detection with high SNR, as well as efficient use of the magnetization, are needed for in vivo hyperpolarization studies.

References

1. Santarelli, M.F.; Positano, V.; Martini, N.; Valvano, G.; Landini, L. Technological Innovations in Magnetic Resonance for Early Detection of Cardiovascular Diseases. Curr. Pharm. Des. 2016, 22, 77–89, doi:10.2174/1381612822666151109112240.
2. Santarelli, M.F.; Martini, N.; Positano, P.; Landini, L. Models and Methods in Cardiac Imaging for Metabolism Studie. Curr. Pharm. Des. 2014, 20, 6171–6181, doi:10.2174/1381612820666140417114122.
3. Van Ewijk, P.A.; Schrauwen-Hinderling, V.B.; Bekkers, S.C.A.M.; Glatz, J.F.C.; Wildberger, J.E.; Kooi, M.E. MRS: A noninva-sive window into cardiac metabolism. NMR Biomed. 2015, 28, 747–766, doi:10.1002/nbm.3320.
4. Shulman, R.G.; Rothman, D.L. 13C NMR of intermediary metabolism: Implications for systemic physiology. Annu. Rev. Physiol. 2001, 63, 15–48, doi:10.1146/annurev.physiol.63.1.15.
5. Ardenkjaer-Larsen, J.H.; Fridlund, B.; Gram, A.; Hansson, G.; Hansson, L.; Lerche, M.H.; Servin, R.; Thaning, M.; Golman, K. Increase in signal-to-noise ratio of >10,000 times in liquid-state NMR. Proc. Natl. Acad. Sci. USA 2003, 100, 10158–10163, doi:10.1073/pnas.1733835100.
6. Haase, A.; Odoj, F.; Von Kienlin, M.; Warnking, J.; Fidler, F.; Weisser, A.; Nittka, M.; Rommel, E.; Lanz, T.; Kalusche, B.; et al. NMR probeheads for in vivo applications. Concepts Magne. Reson. 2000, 12, 361–388, doi:10.1002/1099-0534(2000)12:6.
7. Sánchez-Heredia, J.D.; Olin, R.B.; McLean, M.A.; Laustsen, C.; Hansen, A.E.; Hanson, L.G.; Ardenkjær-Larsen, J.E. Multi-site benchmarking of clinical 13C RF coils at 3T. J. Magn. Reson. 2020, 318, 106798, doi:10.1016/j.jmr.2020.106798.
8. Skinner, J.G.; Menichetti, L.; Flori, A.; Dost, A.; Schmidt, A.B.; Plaumann, M.; Gallagher, F.A.; Hövener, J.-B. Metabolic and Molecular Imaging with Hyperpolarised Tracers. Mol. Imaging Biol. 2018, 20, 902–918, doi:10.1007/s11307-018-1265-0.
9. Adamson, E.B.; Ludwig, K.D.; Mummy, D.G.; Fain, S.B. Magnetic resonance imaging with hyperpolarized agents: Methods and applications. Phys. Med. Biol. 2017, 62, R81–R123, doi:10.1088/1361-6560/aa6be8.
10. Ardenkjaer-Larsen, J.H.; Leach, A.M.; Clarke, N.; Urbahn, J.; Anderson, D.; Skloss, T.W. Dynamic nuclear polarization po-larizer for sterile use intent. NMR Biomed. 2011, 24, 927–932, doi:10.1002/nbm.1682.

11. Ardenkjaer-Larsen, J.H. On the present and future of dissolution-DNP. J. Magn. Reson. 2016, 264, 3–12, doi:10.1016/j.jmr.2016.01.015.
12. Singh, J.; Suh, E.H.; Sharma, G.; Khemtong, C.; Sherry, A.D.; Kovacs, Z. Probing carbohydrate metabolism using hyperpo-larized 13C-labeled molecules. NMR Biomed. 2019, 32, e4018, doi:10.1002/nbm.4018.
13. Wang, Z.J.; Ohliger, M.A.; Larson, P.E.Z.; Gordon, J.W.; Bok, R.A.; Slater, J.; Villanueva-Meyer, J.E.; Hess, C.P.; Kurhanewicz, J.; Vigneron, D.B. Hyperpolarized 13C MRI: State of the Art and Future Directions. Radiology 2019, 291, 273–284, doi:10.1148/radiol.2019182391.