Hyperpolarized 13C-Magnetic Resonance Spectroscopy
Are We Ready for Metabolic Imaging?
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Myocardial metabolic abnormalities have been demonstrated widely in diverse cardiac diseases. Metabolic impairment may be secondary to the underlying pathophysiological mechanism; however, in most conditions, it could be considered a direct cause, or at least a cofactor, in the functional abnormalities of the heart.

A more complete understanding of the myocardial metabolic changes associated with cardiac diseases may lead to pharmacological studies and potentially new metabolic-targeted drugs. In heart failure, agents that act through the optimization of cardiac metabolism may be particularly attractive as they could potentially work without exerting negative hemodynamic effects; this would allow for their addition to current therapies.1 It has been demonstrated that shifting the metabolic substrate of the heart from fatty acids to carbohydrate oxidation can improve pump function and delay the progression of heart failure.2 That said, in spite of the initial enthusiasm over drugs that showed promising metabolic effects in vitro, few clinical benefits have been unequivocally demonstrated. A robust imaging technique, which would allow the direct assessment of metabolism in vivo, is essential to understanding the metabolic changes and the effectiveness of pharmacological drugs. Unfortunately, nuclear medicine techniques, such as positron emission tomography and single photon emission computed tomography, are unable to detect the metabolized tracers and distinguish between different downstream metabolites.3

Magnetic resonance spectroscopy (MRS) with hyperpolarized 13C-enriched substrates is a promising imaging technique for the evaluation of cardiac metabolism in vivo. Because the natural amount of 13C in biological tissue is low, a sufficient signal:noise ratio for 13C-MRS is obtained by increasing the polarization level (hyperpolarization) of these compounds. Currently, dynamic nuclear polarization is the most widely used hyperpolarization technique for 13C-enriched molecules and this enables an increased signal:noise ratio of ≈10000-fold.4 13C-MRS allows for a semiquantitative assessment of substrate changes in a target tissue and real-time measurements of metabolic fluxes.5 6

An understanding of the metabolic pathways involved helps to inform the potential use of the 13C-enriched techniques. Pyruvate, which contains 3 carbon atoms, is the most used 13C-enriched molecule. Pyruvate is a key metabolic substrate that is involved in different metabolic pathways; depending on the position of the 13C-label, one may detect abnormalities in key enzymes involved in pyruvate oxidation and Krebs cycle fluxes: [1-13C]pyruvate leads to[1-13C]-lactate by lactate dehydrogenase, [1-13C]bicarbonate by pyruvate dehydrogenase complex, [1-13C]-alanine from alanine aminotransferase. [2-13C]pyruvate yields other substrates and can be used to assess the enzymatic fluxes in the Krebs cycle, such as [5-13C]glutamate, [1-13C]citrate, and[1-13C]acetylcoenzyme A.7 [3-13C]pyruvate has a short T1, which does not allow for adequate assessment.

In this issue of Circulation: Cardiovascular Imaging, the elegant study by Dodd et al5 demonstrates the application of hyperpolarized 13C-MRS when studying the interaction between metabolic and cardiac functional impairment. In this study, the authors assessed the metabolic changes that occur in the cardiac mitochondrial function using hyperpolarized [1-13C] and [2-13C]-pyruvate; the experiment used surgically induced myocardial infarction in rats. Remarkably, this study links the changes in cardiac metabolism with the progression of heart disease, specifically at 6 and 22 weeks after the infarction. Only at 22 weeks did the authors find a significant relationship between the pyruvate dehydrogenase flux, assessed by [1-13C]pyruvate spectra and the ejection fraction; metabolites of [2-13C]pyruvate were already decreased after 6 weeks, which significantly correlated with the ejection fraction. The authors concluded that at 6 weeks after infarction, acetyl-CoA is normally produced by pyruvate dehydrogenase, but its oxidation is reduced by a decrease in the Krebs cycle activity. At 22 weeks, both acetyl-CoA production and oxidation by pyruvate dehydrogenase decreased. Furthermore, these results of in vivo activity with 13C-MRS were confirmed by results from ex vivo enzyme activity assays and sophisticated measurements of the pool size of the molecules in frozen cardiac tissue. Although descriptions of the defects in the Krebs cycle activity after myocardial infarction are not novel, this study highlighted the potential use of 13C-MRS with hyperpolarized 13C-enriched substrates for the in vivo assessment of metabolic alterations.

On the technical side, 13C-MRS could be performed using different approaches: the 1-dimensional (1D) dynamic MRS method consists of a slice-selective pulse-and-acquire sequence of a single section of the heart, at the highest temporal resolution, and a signal-to-noise/time plot is obtained for each metabolite; the 2D dynamic MRS is acquired with lower temporal resolution than the 1D but allows color maps for each metabolite, which may be superimposed on the

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anatomic proton images of the heart; and for 3D, a single point, or dynamic MRS, which has recently been used for hyperpolarized 13C studies, which covers the heart with multiple voxels in multiple planes, allowing for repeated acquisition over time. Despite the significant scarcity in hyperpolarized 13C spectra, an elevated spectral resolution is required for most of the proposed 13C-substrates to properly separate the contribution of the metabolites of interest. To date, several approaches have been set up to improve the relationship between the signal-to-noise ratio and the temporal resolution in MRS imaging studies.10

Dodd et al used a 7T horizontal small animal MRI scanner, which permitted acquisition of high-resolution 1D 13C-MRS spectra of [2-13C]pyruvate metabolites, that is, [5-13C]glutamate, [1-13C]citrate, and [1-13C]acetyl carnitine. [1-13C]pyruvate can be studied with sufficient resolution using a clinical 3T MRI scanner. Several important studies have been performed with [1-13C]pyruvate using a 3T clinical scanner in models of cardiac diseases in pigs, including myocardial infarction, ischemia/reperfusion, and pacing-induced heart failure.11,12 Although small animal models provide significant insights into human cardiac pathophysiology, rodent and human hearts differ in their architecture, heart rates, oxygen consumption, contractility, protein expression, and even stem cell populations.13 The pig is usually the preferred model in cardiac disease because pigs and humans have similar cardiac size, physiology, and coronary anatomy. Furthermore, cardiac conditions, such as ischemic disease, may have regional myocardial involvement, which will only be adequately assessed by generating 2D or 3D metabolic maps of 13C-MRS imaging in pigs. Ball et al14 demonstrated the feasibility of 13C-MRS imaging in the isolated rat heart, but the technological requirements are a long way from allowing translation to in vivo rat studies. An important aspect is the translatable value of the technological improvements of 13C-MRS (in pigs studies), particularly in coil design, radiofrequency sequence optimization, and 13C-kinetic modeling. Of particular interest in 13C-MRS techniques are the questions on coil design, the signal-to-noise improvement and homogeneity, and the choice of surface coil or volumetric coil. Because 13C-MRS is essentially a semiquantitative technique, the signal:noise ratio for the spectra acquired in different myocardial segments should be homogeneous to obtain accurate measurements. The signal:noise ratio of the surface coils is higher than that of volumetric coils, but decreases with the distance from the coil. Surface coils work only in reception and require an external transmission coil. The need to improve signal detection performed with multichannel surface coils has led us to test different transmitting and receiving coil configuration. This set up, used in pig studies, may be applicable to future assessment in humans.15

Other 13C-enriched molecules (other than pyruvate) have been tested in cardiac studies as surrogates for short-chain fatty acid metabolism.16,17 More than 95% of the ATP formed in the heart, which fuels contractile shortening and ion pumps of the sarcoplasmic reticulum and sarcolemma, is derived from mitochondrial oxidative phosphorylation. This energy comes from electrons transferred from reactions that generate NADH and FADH2, which are derived primarily from the fatty acid β-oxidation pathway, the citric acid cycle, and, to a lesser extent, pyruvate dehydrogenase reaction and glycolysis.18 For this reason, 13C-acetate and 13C-butyrate were used as metabolic probes for short-chain fatty acid metabolism. Although the compartmentalization of the 13C-acetate was recently confirmed, as for 13C-acetate in positron emission tomography, several limitations have been recorded. These limitations arise mainly from the kinetics of conversion, the low signal-to-noise ratio by the use of a volume coil, and a limited amount of 13C (≈5–6x lower in pigs) compared with small animal studies.16 However, hyperpolarized butyrate is characterized by an initial low level of 7% polarization. This leads to a better understanding of the multistep metabolism into ketone bodies, acetoacetate, and several intermediates of the Krebs cycle in small animals; it is characterized by low fluxes of conversion and significant spectral density, comparable with [2-13C]pyruvate.

Taking into consideration its pros and cons, the question arises whether myocardial metabolic assessment by MRS with hyperpolarized 13C-pyruvate is ready for clinical use. The Food and Drug Administration recently approved hyperpolarized [1-13C]pyruvate for clinical studies of prostate cancer; the first human study of [1-13C]pyruvate in prostate cancer was recently performed.19 Hyperpolarized 13C-MRS methods could be made available for human studies of cardiovascular disease in the near future. However, cardiac contractility, flow disturbance, and the effect of the surrounding lung make cardiac applications of 13C-MRS challenging. The technological advances in terms of improved methods for acquisition and reconstruction, hardware configuration, and design will therefore be a crucial component as recently demonstrated by the development of ECG gated multislice pulse sequences.9 In conclusion, 13C-MRS is a promising candidate as a novel imaging tool for the evaluation of the regional metabolic changes in the contracting heart. However, many technological improvements are needed to translate this new imaging tool to the clinical setting.

Disclosures

None.

References


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