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Super cool imaging of energy metabolism in the heart

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Abstract

Evidence supports the hypothesis that the changes in the way the heart uses fuel may be causative in the pathogenesis of heart failure (HF) and treatments that target these metabolic changes are a promising direction for improving outcomes. We have recently demonstrated an augmented form of magnetic resonance imaging (MRI) that gives metabolic information about the human heart, providing a potential new tool to guide the management of patients at risk of developing HF. The ^{13}C images, which show biochemical reactions within cardiomyocytes, are made after the injection of an intravenous contrast agent that is prepared using a recently developed method known as dynamic nuclear polarization (DNP). The addition of ^{13}C imaging only lengthens a routine MRI examination by approximately 10 minutes, giving metabolic information that would complement the wealth of other parameters that can currently be measured using cardiovascular MRI, including structure, perfusion, and pump parameters. ■ *Heart Metab*. 2018;77:37-39

Keywords: cardiomyocytes; dynamic nuclear polarization; heart failure; MRI

Introduction

An increasing body of evidence has emerged to support the hypothesis that the changes in the way the heart uses fuel may be causative in the pathogenesis of heart failure (HF).[1,2] Although radiotracer methods have added a great deal to our understanding of substrate utilization in the heart and have been used to show abnormal energy metabolism in patients,[3-5] there remain gaps in our understanding and room for less invasive imaging methods.

We have recently demonstrated an augmented form of magnetic resonance imaging (MRI) that gives metabolic information about the human heart,[6] providing a potential new tool to guide the management of patients at risk of developing HF. The new method, hyperpolarized ^{13}C MRI, enables imaging of biochemical reactions occurring within cells, including the flux of pyruvate into the tricarboxylic acid (TCA) cycle. The ^{13}C images, which show biochemical reactions within cardiomyocytes *(Figure 1)*, are made after injection of an intravenous contrast agent prepared using a recently developed method known as dynamic nuclear polarization (DNP), which results in an intravenous contrast agent that is "hyperpolarized." In the hyperpolarized state, the molecules in the solution are magnetized such that they produce a strong signal that can be imaged with MRI, even at low (micromo-

Abbreviations

DNP: dynamic nuclear polarization; **HF:** heart failure; **MRI:** magnetic resonance imaging; **PDC:** pyruvate dehydrogenase complex; **TCA:** tricarboxylic acid

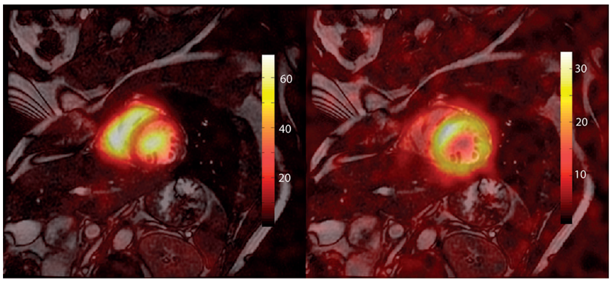

Fig. 1 *Representative human ^{13}C images. The color overlays are the metabolite signals, on top of grayscale anatomical images in a mid-left ventricle slice. The [1-^{13}C]-pyruvate substrate was seen mainly in the blood pool within the cardiac chambers (left). Flux of pyruvate through the pyruvate dehydrogenase complex is reflected in the ^{13}C-bicarbonate images (right), with the signal predominantly in the wall of the left ventricle. The ^{13}C images were scaled so that pixel values represent the signal-to-noise ratio.*

lar) concentrations. The signal enhancement resulting from the DNP process (>10 000-fold) gives enough signal to enable the time-resolved imaging of pyruvate being converted into metabolic products in vivo.

The hyperpolarized state decays with an exponential time constant of 65 seconds, necessitating a rapid injection and fast MRI methods. While this short timescale is technically challenging, it also makes the method particularly feasible to apply in patients as an add-on to clinical cardiovascular MRI protocols. The addition of ^{13}C imaging only lengthens a routine MRI examination by approximately 10 minutes, giving metabolic information that would complement the wealth of other parameters that can currently be measured using cardiovascular MRI, including structure, perfusion, and pump parameters.

The MR signals that result from this method are interesting because abnormal energy metabolism is a well-known feature of the failing heart. A potential application of this imaging method is to have a better understanding of the changes in cardiac metabolism associated with therapies that slow the progression of HF and improve cardiovascular outcomes.[7]

Dynamic nuclear polarization and dissolution

Dynamic nuclear polarization and dissolution (DNP-dissolution) is a recently developed method for creating a new class of contrast agents for MRI.[8-10] The technique results in a sterile solution that is "hyperpolarized," having a degree of spin alignment that is more than 5 orders of magnitude higher than normally achieved within a 3T MRI system. Various MR-active nuclei can be hyperpolarized using DNP-dissolution, but the vast majority of work has used ^{13}C-labelled molecules to enable imaging of biochemical reactions in vivo, such as the enzymatic reactions involved in cellular metabolism.

For human studies, the sample is polarized and dissolved entirely within a sealed, sterile fluid path (SFP) that is discarded after each human dose. Before the start of the hyperpolarization process, the sample vial, at one end of the SFP, is filled with a mixture of the ^{13}C-labelled metabolite of interest (typically [1-^{13}C]-pyruvic acid) and 15 mM of a substance known as AH111501. The purpose of the added AH111501 is to provide the free electron that is the source of the polarization, which is transferred to the ^{13}C nuclei during the DNP process, which occurs at a temperature of 0.8 K.

The mixture of [1-^{13}C]-pyruvic acid and 15 mM AH111501 sodium salt is polarized for approximately 180 minutes to achieve maximal polarization. The hyperpolarized pyruvate is typically dissolved to a concentration of 250 mM. This sterile solution is injected intravenously, and the data acquisition is started immediately.

A ^{13}C spectrum acquired several seconds after the injection contains peaks corresponding to the injected pyruvate, but also from products of the reaction between pyruvate and several enzymes involved in cellular metabolism.[11-16] These other peaks are shifted in frequency due to the change in the molecular structure surrounding the ^{13}C nucleus after its enzymatic conversion into other species.

Imaging HF progression

In preclinical experiments, we aimed to characterize cardiac energy metabolism during HF progression, using hyperpolarized ^{13}C MR alongside conventional methods. HF was induced in pigs (n=5) by right ventricular pacing at 188 bpm for 5 weeks. Pigs were examined noninvasively with MR at weekly time points: cine MRI assessed cardiac structure and function, hyperpolarized [2-^{13}C]-pyruvate was administered intravenously to monitor Krebs cycle kinetics via ^{13}C-glutamate production, ^{31}P MRS assessed cardiac energetics, and hyperpolarized [1-^{13}C]-pyruvate was administered for MRI of pyruvate dehydrogenase complex (PDC) flux via $H^{13}CO_{3-}$ (bicarbonate) production. At the end time point when the pigs developed HF, the myocardium was harvested for biochemical analysis.

At baseline, the pigs had a normal left ventricular cardiac index and end diastolic volume. After 1 to 2 weeks of pacing, cardiac index decreased by 25%, PCr/ATP decreased by 26%, and most interestingly, ^{13}C-glutamate production decreased by 51%. In failing hearts (after 4 to 5 weeks of pacing), end diastolic volume increased by 40% and PDC flux decreased by 67%.

Conclusions

Preclinically, ^{13}C imaging enabled observation of early changes to the Krebs cycle (via alterations in glutamate production) and to cardiac energetics. Carbohydrate oxidation via PDC was maintained until the onset of HF. The method has recently been translated to humans and has the potential to become an important tool for understanding the changes in myocardial metabolism that occur in patients as HF progresses and for developing new treatments. ■

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