Biochemical Specificity in Human Cardiac Imaging by $^{13}$C Magnetic Resonance Imaging

Craig R. Malloy, A. Dean Sherry

Energy contained in lactate, glucose, ketones, and fatty acids is captured by metabolic processes in the heart to produce mechanical and electric work. The actual contribution of each substrate to energy production and the specific metabolic pathways involved is sensitive to both physiological conditions and disease. This knowledge of cardiac biochemistry is derived primarily from studies in isolated hearts and from invasive in vivo studies in experimental animals. Animal models of some diseases, notably acute ischemia and reperfusion, provided valuable insights, but in general, the relevance of animal studies to human disease is uncertain because it is difficult to meaningfully model heart failure, hypertrophy, cardiomyopathies, hibernating myocardium, and other complex conditions. Methods to quantify biochemical events in the heart are important because it is becoming increasingly apparent that chronic adaptations in metabolism may drive processes with adverse consequences, such as impaired energy capture and oxidative stress. Positron tomography provides some metabolic information in patients. However, in spite of the popularity and the high sensitivity for detecting the positron tomography signal does not inherently provide some metabolic information in patients. However, in spite of the popularity and the high sensitivity for detecting the positron tomography signal does not inherently provide some metabolic information in patients. However, in spite of the popularity and the high sensitivity for detecting the positron tomography signal does not inherently provide some metabolic information in patients. However, in spite of the popularity and the high sensitivity for detecting the positron tomography signal does not inherently provide some metabolic information in patients. However, in spite of the popularity and the high sensitivity for detecting the positron tomography signal does not inherently provide some metabolic information in patients. However, in spite of the popularity and the high sensitivity for detecting the positron tomography signal does not inherently provide some metabolic information in patients. However, in spite of the popularity and the high sensitivity for detecting the positron tomography signal does not inherently provide some metabolic information in patients. However, in spite of the popularity and the high sensitivity for detecting the...
conscious, resting person (Figure 1B). The positive results are exciting, but what does it mean to detect HP [13C]bicarbonate? Because pyruvate is metabolized in the heart overwhelmingly via pyruvate dehydrogenase, the appearance of HP [13C]bicarbonate in principle serves as a reliable imaging biomarker for flux through this enzyme. Pyruvate dehydrogenase is a large, multienzyme complex that resides exclusively in mitochondria, so presumably the appearance of [13C]bicarbonate indicates intact mitochondria. After prolonged ischemia and reperfusion, the absence of a HP [13C]bicarbonate has been attributed to cardiomyocyte injury. In a model of pacing-induced heart failure, the bicarbonate signal decreased late in the evolution of heart failure. However, in general, the absence of a [13C]bicarbonate signal should be interpreted cautiously because high plasma concentrations of fatty acids or ketones—exactly the situation to be anticipated in sick patients—will suppress oxidation of HP [1-13C]pyruvate even with normally functioning mitochondria.

An important challenge going forward is to investigate and validate methods to quantify flux in pyruvate dehydrogenase and the other pathways involved with pyruvate metabolism.

HP [13C] imaging of the human heart has limitations and disadvantages. The method requires an expensive external device to generate hyperpolarized materials that must be immediately adjacent to the MR scanner. Transfer of the polarized material to the subject must occur within 30 to 50 seconds (Figure 1A). Current 13C coils, acquisition schemes, and reconstruction algorithms are almost certainly suboptimal. These limitations are primarily technical, and more advanced coils and acquisition schemes will certainly improve image quality. In particular, it is important to assure that signals can be reliably compared from different regions of the myocardium. For example, in Figure 2, there is some variation in HP [13C]bicarbonate signal—does this indicate true differences in metabolism and perfusion of the septum or does it reflect differences in how the coil interacts with tissue in these regions? Once these technical limitations are solved, HP [1-13C]pyruvate will likely provide other insights into metabolism that are simply not available to clinicians today. For example, the [1-13C]lactate signal generated from HP [1-13C]pyruvate occurs largely through an exchange reaction in the active site of lactate dehydrogenase, so it reflects the size of the existing tissue lactate pool, not newly generated lactate from pyruvate. This is important because it offers the potential to image lactate pool sizes in different tissue regions within a few seconds after injection of HP [1-13C] pyruvate. This could potentially allow rapid imaging of tissue ischemia and, in addition, allow monitoring of newly generated lactate after a pharmacological intervention. It must be remembered that the mass of injected [1-13C]pyruvate is significant and potentially could influence cardiac metabolism. Although HP methods provide a new window into cardiac metabolism, it will be important to validate, to the extent possible, with well-accepted existing methods to evaluate metabolism, such as positron tomography and other techniques.

This study demonstrates 2 important points. First, currently available technologies, including the SPINlab as well as radiofrequency coils and pulse sequences, are at least sufficient to begin studies of the myocardium in human subjects. Second, metabolism of [1-13C]pyruvate to downstream metabolites, such as [13C]bicarbonate, can be detected in normal human myocardium, opening the opportunity for better understanding of metabolism in high-impact myocardial disease. Additional 13C-enriched metabolic probes for interrogating other pathways in the heart, such as [1-13C]lactate (see Figure), will likely become available. Because the method inherently provides detailed chemical information about the 13C-enriched probes, it is possible to copolarize 2 compounds, one targeting metabolic processes and the other measuring myocardial perfusion. If the technology can be refined, there are benefits over current methods for a clinician: the absence of ionizing radiation, the capacity to integrate with any other cardiac MR examination, and access to specific information about cardiac metabolism that is not provided by radionuclide methods.

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None.
References


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