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Measuring myocardial energetics with cardiovascular magnetic resonance spectroscopy

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Key Points

- Dysfunction of multiple important myocardial metabolic pathways and energetics occurs with several common cardiovascular diseases.
- Because myocardial metabolism fuels ongoing cardiac contractile function, metabolic and energetic abnormalities in the failing heart may contribute to contractile dysfunction, disease development, and progression.
- Cardiac magnetic resonance spectroscopy allows the non-invasive, non-destructive exploration of metabolism in the beating heart.

Synopsis

The heart has the highest energy demands per gram of any organ in the body and energy metabolism fuels normal contractile function. Metabolic inflexibility and impairment of myocardial energetics occur with several common cardiac diseases, including heart failure and in the ischemic heart. This review explores several decades of innovation in cardiac magnetic resonance spectroscopy modalities and their use to non-invasively identify and quantify metabolic derangements in the normal, failing, and diseased heart. The implications of this non-

invasive modality for predicting significant clinical outcomes and guiding future investigation and therapies to improve patient care are discussed.

1. Introduction

This review summarizes the cardiac metabolic remodeling that occurs in major cardiac diseases and the advantage of quantifying metabolism noninvasively in the beating heart with cardiac magnetic resonance spectroscopy (CMRS).

2. Primer on Myocardial Metabolism

Most of myocardial chemical energy is derived from the oxidation of the three main substrates, free fatty acids (FFA), glucose and ketone bodies¹. Glucose and FFA are catabolized into acetyl-CoA to enter the mitochondrial tricarboxylic acid (TCA, Krebs) cycle. ATP formation is then completed by mitochondrial oxidative phosphorylation. The creatine kinase (CK) reaction is the main cardiac energy reserve reaction which reversibly transfers the high energy phosphate (HEP) of ATP to creatine (Cr) to form creatine phosphate (PCr):

Where k_r is the reverse rate constant and k_f is the forward rate constant of CK activity.

Myocardial bioenergetics have been defined by HEP levels and their turnover in tissue. Thus, the CK reaction by producing PCr, may enhance intracellular delivery of high-energy phosphate from mitochondrial sites of ATP production to cytoplasmic sites of ATP utilization but CK is also thought to act as a temporal HEP buffer tightly maintaining high ATP and low ADP concentrations during changes in energy demand (**Figure 1**)².

Remodeling of certain metabolic pathways, substrate preferences and PCr:ATP energy balance occur with several common cardiovascular diseases, including heart failure, and may contribute to disease development and progression³. Myocardial ATP turnover depends in large

part on energy demand and thus *in vitro* studies may not always faithfully recapitulate the energetic profile of the *in vivo* contracting heart. Therefore, the non-destructive exploration and quantification of metabolism in the beating heart with cardiac CMRS offers unique and potentially powerful means to better understand the role of altered metabolism in cardiac diseases and develop novel diagnostic and therapeutic targets.

3. Cardiac Magnetic Resonance Spectroscopy Principles

CMRS allows the non-invasive measurement of proton (^1H)-containing metabolites such as Cr, carbon (^{13}C)-containing metabolites from glucose and lipid metabolism, and phosphorus (^{31}P)-containing metabolites such as PCr and ATP. Those nuclei have an intrinsic nuclear magnetic moment, which is called nuclear spin. These nuclear spins will be aligned with or against an applied magnetic field (B_0), leading to a macroscopic equilibrium magnetization (M_0) along B_0 . Radiofrequency (RF) pulses can be used to perturb the alignment of M_0 , so called excitation. The excited magnetization will then precess around B_0 and induce a measurable voltage in receiver coils tuned to the specific nucleus. The precession frequency depends on B_0 , the nucleus, and its chemical environment enabling the identification of different metabolites. The detected signal is transformed to a spectrum using the Fourier transformation to identify the different frequency components of the signal. *In the spectrum, different metabolites are then identified by the frequency of their signal peaks, and the area under the peak reflects the concentration of that metabolite (Figure 2).* Today, CMRS is typically performed using scanners with B_0 of 4.7⁴ or 11.7⁵ tesla (T) in cardiac preclinical applications and 1.5 T⁶, 3 T⁷ or 7 T⁸ in clinical studies.

3a. ^{31}P -MRS

^{31}P -MRS is most commonly used in studies of myocardial energy metabolism and the techniques for spatial-localization often include either 1-, 2-, or 3-dimensional chemical shift

imaging (CSI) or image-selected *in vivo* spectroscopy (ISIS). ³¹P-MRS is the only technique able to non-destructively measure HEP in the *in vivo* human heart (**Figure 2**).

The cardiac PCr/ATP ratio was the first myocardial energetic parameter measured with spatially-localized ³¹P-MRS^{6,9,10} and PCr is roughly twice as abundant as ATP in the healthy human heart. Absolute quantification of PCr and ATP concentrations can be accomplished by comparison to an external standard and the results do not assume that ATP is constant^{11,12,13}. A summary of major ³¹P-MRS absolute phosphate metabolites render concentrations of PCr = 9.9±0.7 and ATP = 6.0±0.5 μmol/g wet wt in the healthy human heart^{11–20,7}.

Furthermore, measurement of uni-directional ATP synthesis through the CK reaction (“CK flux”) with ³¹P saturation transfer MRS offers critical insight into energy turnover in cardiomyocytes. The conventional saturation transfer approach consists of saturating the magnetization of γ-P of ATP involved in the chemical exchange with PCr, which leads to a decrease of the PCr magnetization (M₀′) proportional to pseudo first-order rate constant, *k_f*, and calculated as follows:

$$k_f = \frac{1}{T_1'} \left(1 - \frac{M_0'}{M_0}\right)$$

With *T₁*′ being the longitudinal relaxation time and M₀′ and M₀ the equilibrium magnetizations of PCr while γ-ATP is saturated or unsaturated, respectively. With conventional saturation techniques the determination of *T₁*′ is very time consuming, but ~15 years ago accelerated approaches were developed and enabled the first measurements of ATP synthesis in the human heart¹⁷. Multiple techniques have since been used to calculate *k_f* (~0.33sec⁻¹)^{17,21–24}, and subsequently CK flux that equals *k_f* × [PCr] (~3.4 μmol/g/sec) in the healthy human heart^{17,23,24}.

³¹P-MRS can also be used to noninvasively measure inorganic phosphate (Pi), to quantify cytosolic ADP (from the CK equilibrium reaction), intracellular pH (from the chemical shift of Pi relative to PCr) and the free-energy change of ATP hydrolysis [-Δ*G*_{ATP} (kJ/mol)]^{17,25}. While these approaches have been used extensively in isolated, perfused hearts, they have been less

successful and less commonly implemented in the human heart, due to overlap of blood 2,3-diacylglycerol (DPG) resonances with the Pi resonance used for most calculations. The peak overlap may be overcome by the increased chemical shift dispersion at 7 T^{8,26}.

3b. ¹H-MRS

Spatially-localized ¹H-MRS has been used to measure a number of metabolites²⁷ but *in vivo* human studies are primarily limited to measuring myocardial triglycerides^{28,29} and total creatine³⁰. Unlike ¹³C and ³¹P-MRS which require specially-tuned excitation and detection coils, conventional imaging surface coils can be used for ¹H-MRS.

3c. ¹³C-MRS

Although ¹³C-MRS is a powerful technique used to study carbon substrate metabolism in animal hearts, it is rarely used in human hearts due to the low sensitivity of the ¹³C nucleus and the expense of ¹³C-labeled substrates. However, dynamic nuclear polarization, an innovative technique, theoretically improves sensitivity 10,000-fold³¹. Metabolites labeled with ¹³C are hyperpolarized in a polarizer and then injected into a living system^{32,33}. Although the entire process is complex in practice and the hyperpolarization is short-lived, this technique allows real time assessment of the Krebs Cycle³⁴ and may soon be applicable in people³⁵.

4. Applications

4a. Heart failure risk factors: Ischemia, Infarction, and Diabetes

Early ³¹P-MRS studies in isolated animal hearts during acute, severe ischemia demonstrated rapid and significant decreases in PCr and increases in Pi with initially preserved ATP^{36,37,38}. ATP decline appears after prolonged ischemia and PCr depletion, but the PCr signal recovers rapidly during reperfusion in viable tissue³⁹.

³¹P-MRS has also been utilized *in vivo* to detect energetic changes during myocardial ischemia in humans⁴⁰. During isometric handgrip exercise (IHE) stress, spatially-localized ³¹P-

MRS detected significant stress-induced reductions in cardiac PCr/ATP in patients with significant coronary artery disease, but not in healthy subjects or those with non-ischemic disease. Furthermore, stress-induced myocardial PCr/ATP decline resolved after successful revascularization⁴⁰. These observations of IHE stress-induced declines in cardiac PCr/ATP in CAD patients were reproduced by others^{41,42}.

The chronic disruption of myocardial metabolism following infarction has been identified with ³¹P-MRS whereby viable myocardium (more PCr and ATP)^{12,43}, ischemic without infarction (intermediate PCr and ATP)¹², and scarred post-infarct (less PCr and ATP)^{12,43} myocardium can be distinguished⁴³. ¹H-MRS can detect lower creatine in infarcted areas throughout canine⁴⁴ and human hearts³⁰ and ³¹P-MRS saturation transfer techniques identified reduced CK flux in infarcted myocardial regions¹⁹.

³¹P-MRS has identified reduced PCr/ATP in myocardium of patients with risk factors for heart failure such as those with hypertension with diastolic dysfunction⁴⁵, type 2 diabetes^{46,47}, type 1 diabetes⁴⁸ and/or obesity⁴⁹. Moreover, ¹H-MRS assessed decreased creatine in the myocardium of various nonischemic heart diseases⁵⁰.

4b. Heart Failure

Heart failure (HF) is often defined as the inability of the heart to pump sufficient blood to meet the demands of the body (or to do so at elevated filling pressures) and the decades old energy-deprivation hypothesis of HF⁵¹ posits that the failing heart has insufficient metabolic energy to fuel normal contraction. The emergence of MRS measures of energy metabolism in the beating heart have addressed several gaps in this theory.

Early animal and human tissue studies⁵² supported the energy-starvation hypothesis whereby progressive and insidious loss of ATP with a loss of the total purine pool, most evident when heart failure is severe, were reported as well as an early reduction in the creatine pool⁵³. Isolated human myocardial tissues are difficult to rapidly obtain, especially in patients with early, mild

disease, but seminal studies demonstrated significant reductions in ATP, total adenine nucleotides, and nicotinamide adenine dinucleotide (NAD)⁵⁴, in creatine content⁵⁵ and in CK activity⁵⁶ in patients with heart failure. Given the invasive nature of tissue biopsies, ³¹P- and ¹H-MRS have been the primary methodologies to better understand cardiac metabolism in HF under physiologic conditions. Several early groups reported a 20%-30% reduction in cardiac PCr/ATP at rest in systolic HF and dilated cardiomyopathy (DCM) patients⁵⁷⁻⁶¹. The subsequent ability to noninvasively quantify HEP concentrations^{11,13} revealed that the PCr/ATP ratio, in fact, may underestimate the reductions observed in absolute concentration of PCr, especially in end-stage heart failure. Cardiac ATP flux through CK is reduced by ~50% in patients with heart failure and non-ischemic dilated cardiomyopathy¹⁷ and by nearly 70% in patients with left ventricular hypertrophy and heart failure¹⁸. Cardiac CK flux declines before ATP loss in human HF and the reduction is greater than changes in absolute metabolite concentrations or PCr/ATP. In addition, extensive energetic abnormalities, including derangements in HEP metabolism^{6,62}, reduced CK flux^{56,17,18,63,64}, and lipid accumulation^{65,66} have been reported in human heart failure.

An early study⁵⁸ demonstrated lower PCr/ATP in aortic valve disease patients with symptomatic heart failure than in those without. Cardiac PCr/ATP was shown to correlate with New York Heart Association functional class of symptom severity in DCM patients, and reported to improve or even normalize with implementation of conventional medical therapy over three months (ACE-inhibitors; Beta-blockers)⁵⁹. In the late 1990s, low cardiac PCr/ATP was found to predict all-cause and cardiovascular mortality in DCM patients⁶⁷. More recently, rates of ATP synthesis through CK, rather than PCr/ATP, independently predicted heart failure related events including transplant and cardiovascular mortality in HF patients on contemporary therapy⁶³. More recently CK flux in heart failure patients was shown to correlate with myocardial mechanical power and mechanical efficiency, suggesting that CK energy

deprivation is closely associated with cardiac dysfunction⁶⁴. Thus, myocardial energetic abnormalities not only occur in heart failure and are related to symptom and functional severity, but predict subsequent adverse cardiovascular outcomes.

Eighty years of cardiac metabolic research has collectively improved our understanding of energetic dysfunction and its contribution to the failing human heart, however many questions remain. Pathways of future investigation of energetics in heart failure include 1) understanding metabolic differences in heart failure with reduced versus preserved ejection fraction, 2) defining biochemical remodeling and myocardial mitochondrial function in a new age of conventional therapy, and 3) developing novel metabolic drug targets.

Limitations and Perspectives

Spatial resolution and depth of detection can limit the application of ³¹P-MRS for heterogeneous diseases such as myocardial infarction. Higher magnetic field strength in clinical applications (7T) will improve signal to noise ratio, accelerate acquisitions, and may allow the exploration of Pi and energetics in small myocardial regions. In addition, the development of chemical exchange saturation transfer and hyperpolarized ¹³C-MRS techniques are very promising techniques to map *in vivo* free creatine, PCr and assess pyruvate dehydrogenase flux. A current gap in the understanding of bioenergetics in heart failure is the evaluation of individuals with heart failure with preserved ejection fraction.

Summary/Discussion

Myocardial energetics are impaired in systolic heart failure and acute ischemia. Metabolic remodeling has been demonstrated in progressive heart failure stages, chronic infarction, and even in conditions associated with increased heart failure risk, including hypertension, diabetes, and obesity. Some energetic abnormalities have been shown to correlate

with symptom severity and significant heart failure outcomes, including mortality. CMRS has been fundamental in building our understanding of energy-deprivation in the failing heart and will likely continue to be a pioneering technology in the development and evaluation of new era heart failure therapeutics with focused metabolic targets.

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Figure

Figure 1: Representation of myocardial energy transport. The CK energy shuttle theoretically provides ATP from mitochondria to the sites of consumption. This includes two main isoforms of CK, mitochondrial (MtCK) and cytoplasmic. Creatine is taken up from blood through Cr transporter (CRT). Adapted from Schlattner *et al*⁶⁸ with permission.

Figure 2. Comparison of spatially localized ^{31}P -MRS of a healthy volunteer (A) and a patient with DCM with significant reduction of PCr (B). Upper images show the 1D CSI localization of ^{31}P -MRS (anterior left ventricular wall). The peaks of the spectra (bottom panel) show the combination of inorganic phosphate (Pi) and 2,3-diphosphoglycerate (DPG), phosphodiesteres, PCr, γ -ATP, β -ATP and α -ATP. From Ingwall and Weiss⁶⁹ with permission.