Metabolic imaging with cardiac magnetic resonance spectroscopy

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Abstract

The only non invasive technique for the assessment of cardiac metabolism in patients that does not use radiation is magnetic resonance spectroscopy (MRS). By interrogating signals from phosphorus-31 and hydrogen-1, spectroscopy offers a wealth of metabolic information on the heart muscle. This review focuses on the two areas of greatest potential for MRS: heart failure and ischemic heart disease. MRS has demonstrated deranged cardiac energetics in patients with heart failure, and this is probably a major mechanism contributing to contractile dysfunction. In ischemic heart disease, altered energetics are a highly sensitive indicator of the presence of myocardial ischemia, offering the prospect of a non invasive biochemical stress test for the heart. Although major technical development is required for the future, cardiac MRS holds great potential for clinical application.
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Introduction

Cardiovascular magnetic resonance is now a well established technique in clinical cardiology and is used to assess cardiac anatomy, function, perfusion, and viability. However, this method only uses the signal from protons in fat and water molecules for image generation. In contrast, magnetic resonance spectroscopy (MRS) allows us to use the signals, not only from protons, but also from other nuclei such as phosphorus-31 (^{31}P) and others (eg, sodium-23, carbon-13) [1–3]. ^{31}P-MRS is the most widely used form of spectroscopy, and it allows detection of adenosine-5'-triphosphate (ATP) and phosphocreatine (PCr), the high-energy phosphate compounds in the heart. ATP is the direct energy source for all energy-consuming reactions in the heart, whereas PCr is the major compound for energy storage and

transport [4]. In principle, many research questions and clinical problems could be addressed by assessing cardiac high-energy phosphate metabolism; however, MRS is currently limited by the fact that MRS signals are approximately a million times weaker than the signals interrogated in magnetic resonance imaging, as a result of the lower concentrations of metabolites and lower magnetic resonance sensitivity of non proton nuclei. Thus the limited temporal and spatial resolution of the method currently limits its clinical application. In spite of these challenges, MRS studies have already contributed enormous insight into the pathophysiology of human heart disease.

Technical considerations

The first reports of human cardiac ^{31}P-MRS are from the 1980s [5]. MRS can be performed on the same

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magnetic resonance systems used for imaging, typically at a field strength of 1.5–3 Tesla (T). There are, however, additional hardware and software requirements, such as a ^{31}P surface coil, a broadband radiofrequency transmitter, spectroscopy pulse sequences, and post-processing software [1,3]. Unlike magnetic resonance imaging studies, most MRS studies have been performed with patients in the prone position, to bring the heart closer to the surface coil. Before starting spectral acquisition, the magnetic field is homogenized with shimming, as MRS places high requirements on field homogeneity. Next, proton scout images are obtained for positioning the spectroscopic voxels over the heart. A range of different localization techniques (eg, 3-dimensional chemical shift imaging) makes it possible to obtain signal almost exclusively from the heart, excluding contaminating ^{31}P signal from neighboring skeletal muscle and liver [3]. Because of the inherent low resolution of MRS, a large number of acquisitions have to be signal averaged, to obtain a magnetic resonance spectrum with an acceptable signal-to-noise ratio. A typical ^{31}P spectrum from a normal individual is shown in *Figure 1*. Resonances are identified for the three phosphorus atoms of ATP (α, β, and γ ATP), PCr, and also 2,3-diphosphoglycerate (2,3-DPG) from blood and phosphodiesters (PDE) from phospholipids. Using line-fit algorithms, the PCr : ATP ratio can be calculated. This is an exquisitely sensitive index of the energetic state of the heart: it decreases within seconds of the onset of ischemia [6], because, when oxygen demand outstrips oxygen supply, PCr concentrations decrease long before ATP concentrations start to decrease. There is, however, a second mechanism that can decrease the PCr : ATP ratio: the reduction in the total creatine pool that occurs in heart failure [4]. Typical technical specifications for cardiac ^{31}P-MRS at 1.5 T

are an acquisition time of 20–40 min, voxel sizes of 20–70 ml and a PCr : ATP ratio variability of approximately 15%. Further developments in MRS methodology will improve these parameters, with a goal of voxel sizes of less than 10 ml, acquisition time less than 10 min, and a measurement variability of less than 10%.

Heart failure

Deranged cardiac energy metabolism is a hallmark of the failing heart [4,7]. Accordingly, PCr : ATP ratios are reduced in heart failure, correlating with the New York Heart Association (NYHA) functional class [8] and left ventricular ejection fraction [9]. Most importantly, they are a strong predictor of prognosis, and in one study the PCr : ATP ratio was a better predictor of long-term survival than NYHA class or left ventricular ejection fraction (*Figure 2*) [10]. Although PCr : ATP ratios are powerful indicators of the extent of energetic derangement in heart failure, they still underestimate the true extent of metabolic derangement. Recent spectroscopy techniques have made the absolute quantification of ATP and PCr possible, showing approximately 50% reduction in PCr and 35% reduction in ATP, with a concomitant 25% decrease in the PCr : ATP ratio, in heart failure [11]. An even more sensitive indicator of deranged energetics may be the dynamic rate of turnover of ATP. Recently, ATP turnover (ATP flux through the creatine kinase reaction) was measured in volunteers and patients with heart failure; for an 18% reduction in PCr concentrations, a 50% reduction in the rate of turnover of ATP was demonstrated [12]. Thus the measurement of ATP turnover rates holds promise as a highly sensitive indicator of energetic derangement in heart failure.
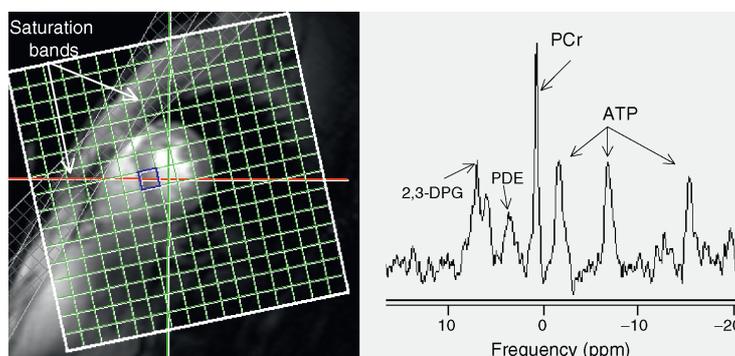

Figure 1. In-vivo human cardiac phosphorus-31 (^{31}P) magnetic resonance spectroscopy, 3-dimensional chemical shift imaging sequence. Left: Short-axis hydrogen-1 magnetic resonance image of the heart with a superimposed grid of spectroscopic voxels. The interrogated cardiac voxel (blue square) is placed in the interventricular septum to avoid contamination from skeletal muscle. Saturation bands are placed over the chest wall skeletal muscle to suppress further any skeletal muscle signal. Right: Example of a cardiac ^{31}P-magnetic resonance spectrum in a healthy individual. Resonances for 2,3-diphosphoglycerate (2,3-DGP), phosphodiesters (PDE), phosphocreatine (PCr), and the three phosphorus atoms of adenosine-5′-triphosphate (ATP) (from left to right: γ, α, and β-ATP) are detectable. 3T Siemens TIM-Trio system. Acquisition matrix size $16 \times 16 \times 8$ voxels, field of view $240 \times 240 \times 200$ mm.
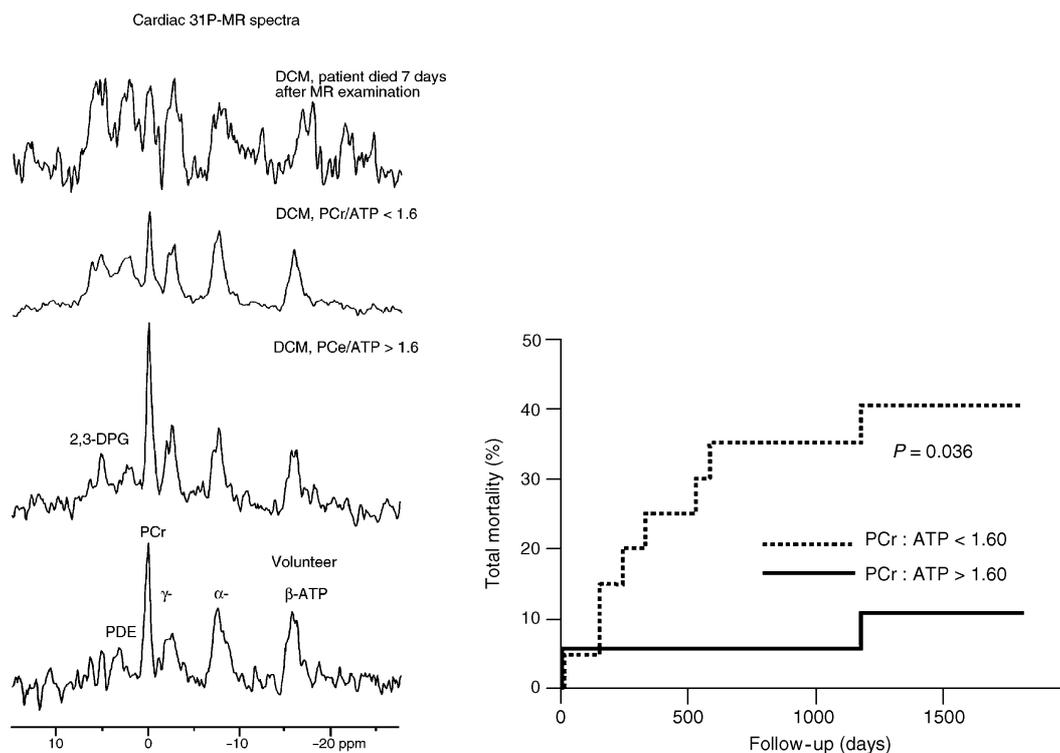
Figure 2. Phosphorus-31 (^{31}P) magnetic resonance spectroscopy in dilated cardiomyopathy. Left: ^{31}P-magnetic resonance spectra in, from bottom upward: a healthy volunteer, a patient with mild dilated cardiomyopathy (DCM), a patient with severe DCM with reduced phosphocreatine (PCr) : ATP ratio, and a patient who died 7 days after the magnetic resonance examination, showing a massive reduction in the PCr : ATP ratio. Right: Kaplan–Meyer curve analysis of total mortality in DCM. Patients were subdivided according to the initial PCr : ATP ratio (greater or less than 1.60). Substantially increased mortality was observed in patients with an initially reduced PCr : ATP ratio. Modified from Neubauer et al. [10], with permission.

An important area is the use of MRS for monitoring energetic changes in the heart after novel forms of treatment of heart failure. Our initial study indicated that conventional treatment of heart failure with β-blockers, angiotensin converting inhibitors, and diuretics for 3 months significantly improved the PCr : ATP ratio, together with clinical improvement [8]. Most recently, a study of the use of the investigational drug, trimetazidine, in patients with heart failure revealed that trimetazidine was associated with a 33% increase in the PCr : ATP ratio, concomitant with improvements in NYHA class and left ventricular ejection fraction [13]. Although currently available studies on this subject are clearly limited by their small size, the concept of monitoring novel drug therapy for heart failure with regards to its effects on cardiac energetics is an extremely appealing one.

Ischemic heart disease

A decrease in PCr concentration and concomitant increase in inorganic phosphate are among the most sensitive indicators of myocardial ischemia, occurring within seconds of the onset of oxygen deprivation [6].

This has led to the concept of a biochemical stress test for patients with suspected coronary disease [1]. Indeed, patients with left anterior descending coronary artery stenosis show significant decreases in PCr : ATP ratio during increased cardiac work, with the ratio returning to normal after recovery. After patients had undergone revascularization by percutaneous coronary intervention or bypass surgery, such decreases could no longer be demonstrated [14]. Furthermore, similar reductions in the PCr : ATP ratio during physical exercise have been observed in female patients with syndrome X [15]. In this cohort, over a period of 3 years, an abnormal ^{31}P-MRS stress test has been demonstrated as a strong predictor of future cardiovascular events [16]. Thus ^{31}P-MRS stress testing is, in principle, an extremely attractive technique for detecting myocardial ischemia at a tissue level, monitoring the anti-ischemic efficacy of medical or interventional therapy, and, potentially, as a tool with which to assess prognosis. The main challenge with studying ischemic heart disease with MRS is that it is spatially heterogeneous, requiring high spatial resolution, so that true clinical applicability will only be achievable once the improvements in technical specifications outlined above have been achieved.

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A second application of MRS in ischemic heart disease is the assessment of viable myocardium. Normal, stunned, and hibernating myocardium show (near) normal concentrations of high-energy phosphates, whereas scar tissue has almost negligible concentrations of high-energy phosphates [17]. Thus, in principle, MRS would be well suited to the assessment of viability [1]. However, with the success of new magnetic resonance imaging techniques such as gadolinium-based late enhancement for viability imaging (spatial resolution 16 microliter), it now seems questionable that this particular application will ever become a success for MRS.

Conclusions and future directions

Magnetic resonance spectroscopy is an extremely interesting technique allowing non invasive, non radiation measurements of cardiac metabolism in the patient. Its future success will undoubtedly depend on further technical development, but if high spatial and temporal resolution can be achieved in addition to high reproducibility of measurements, then widespread application of this method would be predicted. Technical improvement is most likely to come from substantially greater field strengths (eg, 7 T), new phased-array coils, and, at least for carbon-13, with hyperpolarization techniques [18], which are currently entirely experimental, but can, in principle, boost the magnetic resonance signal by a factor of up to 100 000. In addition to heart failure and ischemic heart disease, diabetes [19], obesity [20], and inherited cardiomyopathies [21] are other highly promising areas for novel research into the interrelations of cardiac metabolism and contractile dysfunction by MRS.

Summary

Magnetic resonance spectroscopy allows for the non invasive assessment of various aspects of cardiac metabolism without the use of ionizing radiation. The most promising areas are heart failure and ischemic heart disease. Before the method can find broad clinical application, further technical improvements are necessary that should lead to substantially improved temporal and spatial resolution, and reduced variability of measurement. ■

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