^{31}P cardiovascular magnetic resonance spectroscopy: a unique approach to the assessment of the myocardium

“Cardiovascular magnetic resonance imaging provides cardiac and vascular images with excellent resolution for anatomic structures.”

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Cardiovascular magnetic resonance (CMR) is the most versatile of the diagnostic imaging technology encompassing imaging to assess cardiac morphology, function, perfusion, viability, the coronary arteries and myocardial metabolism [1]. With the development of clinically applicable CMR spectroscopy during the last two decades, noninvasive biochemical/metabolic data have become available. CMR spectroscopy has a minimal risk similar to that of CMR imaging. CMR imaging provides cardiac and vascular images with excellent resolution for anatomic structures and has become a widely applicable diagnostic approach. At present, CMR spectroscopy has been applied only in research.

There are two fundamental questions regarding clinical applicability of CMR spectroscopy. Is the information it provides clinically useful? While the value of the information is incontestable, will CMR spectroscopy prove to be cost effective?

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The major nuclei that have the potential to be used for CMR spectroscopy include proton (^1H), sodium (^{23}Na), carbon (^{13}C), fluorine (^{19}F) and phosphorus (^{31}P). The ^{31}P has been the dominant nucleus for CMR spectroscopy since the first clinical ^{31}P spectra were obtained in the 1980s [2].

Phosphate metabolism is the key to the energy status of the cell. The close relationship between phosphorylated metabolites and function of the

myocardium has made ^{31}P magnetic resonance (MR) spectroscopy an ideal candidate for evaluating the health of the myocardium and skeletal muscle. The metabolites depicted in the myocardial ^{31}P spectrum include: ATP, phosphocreatine (PCr), inorganic phosphate (Pi), phosphomonoesters, phosphodiester and 2,3-diphosphoglycerate (2,3-DPG) in the red blood cells of the ventricular cavity. The chemical shift of the Pi provides a means for determining the intracellular pH (pH_i). *In vivo* ^{31}P MR spectroscopy has demonstrated a multitude of possibilities in studies such as regulation oxidative phosphorylations [3,4], high workload state [5,6], kinetic studies of creatine kinase flux [7] and responses of ischemic myocardium [8]. Recently, ^{31}P MR spectroscopy has been used to examine the bioenergetics after mesenchymal stem cell transplantation [9,10].

The greatest potential for clinical application of ^{31}P CMR spectroscopy is the detection of myocardial ischemia, such as that observed in coronary artery disease. Besides the high-energy phosphate (HEP) in the normal myocardium [11,12], studies using ^{31}P CMR spectroscopy have characterized various myocardial pathologies. It has been demonstrated that a transient imbalance between oxygen supply and demand in myocardium with compromised blood flow results in a decrease in the PCr/ATP ratio during isometric handgrip exercise in patients with myocardial ischemia [13,14]. An abnormal decrease in the PCr/ATP ratio during stress using handgrip exercise was found in some women with symptoms that justified coronary angiography. Such findings by ^{31}P CMR spectroscopy suggested myocardial ischemia in the absence of angiographically

significant coronary artery stenosis [15]. In this population of women, a positive stress ^{31}P CMR spectroscopy also identified women most likely to have rehospitalizations and repeat coronary angiograms [16]. The ^{31}P CMR spectroscopy can also identify viable myocardium where the absolute concentration of ATP content is reduced in nonviable or scar tissue, but remained relatively normal in viable myocardium [17]. Myocardial infarct was examined by creatine kinase ATP supply and correlated with surviving myocytes [18]. Altered cardiac energy metabolism is the characteristic feature of heart failure [19]. Along with the PCr/ATP ratio, creatine kinase reaction examined using ^{31}P saturation transfer can be correlated with clinical severity of heart failure [20].

The endomyocardial biopsy is regarded as the 'gold standard' for the evaluation of rejection, but it is not free of risk. Noninvasive CMR has been suggested to be complimentary to myocardial biopsy. In the rejection evaluation, a significant decrease in PCr/Pi and ATP/Pi was found in hearts showing severe rejection, and a mild decrease in pH was observed. Results obtained by CMR spectroscopy showed a higher level of significance than the MRI findings. Neither CMR imaging nor ^{31}P CMR spectroscopy was able to differentiate between nonrejecting and mildly rejecting hearts, but a combination of both modalities improved the level of significance and the ability to diagnose early rejection in this heterotopic transplant model. Moreover, ^{31}P CMR spectroscopy allows *in vivo* differentiation between cardiac rejection and acute myocardial ischemia. The ^{31}P CMR spectroscopy is well suited to myocardium that shows spatially homogenous pathology, such as in dilated cardiomyopathy [21,22], or in valvular disease showing abnormal PCr/ATP ratio from the entire heart [23,24]. It also showed reduced PCr/ATP ratio in hypertrophic cardiomyopathy [25,26]. Studies

demonstrated that reduced PCr/ATP ratio correlated with markers of diastolic dysfunction in diabetes mellitus [27,28]. We reported that metabolic change observed during stress ^{31}P CMR spectroscopy correlates with the retinopathy as an indicator of the microvascular disease in Type 1 diabetes, as shown in FIGURE 1 [29].

"Findings by ^{31}P cardiovascular magnetic resonance spectroscopy suggested myocardial ischemia in the absence of angiographically significant coronary artery stenosis."

Obtaining high-quality ^{31}P spectra from the heart, however, is an arduous task. The heart is irregularly shaped and is in constant motion during its contractions and from the respiratory cycle. Some heart structures of clinical interest (e.g., atrial or ventricular septa) are small and located deep within the chest, leading to weak signals. The red blood cells within the cardiac blood pool of the chambers give a strong 2,3-DPG signal that interferes with the Pi resonance of the myocardium. Owing to technical characteristics of the resonator, the entire heart cannot be interrogated by surface coil spectroscopy. The weak ^{31}P signal requires a relatively large voxel size that would make examinations for regional heterogeneity very difficult. Furthermore, the metabolic changes measured in the PCr/ATP ratio are not specific for particular disease states (e.g., for myocardial ischemia, myocardial allograft rejection and cardiomyopathy). Such limitations and challenges for ^{31}P CMR spectroscopy need to be addressed by the following measures in order to improve spatial and spectral resolutions and to obtain better reproducibility.

Hardware

For ^{31}P acquisition, multinuclei capability is required, including a broadband frequency transmitter and corresponding coil that resonates at ^{31}P frequency. Surface coils of 5–10 cm in diameter have frequently been used for CMR spectroscopy studies where the tissue is the dominant noise source. If the region of interest is beyond that of the anterior wall of the left ventricle, a highly efficient volume coil is essential. Higher field magnets (≥ 3 tesla [3T]) provide direct benefit of improved signal-to-noise ratio. Improvement in spectral resolution at higher field is even more significant. The Pi peak can be identified in the spectrum at 3T so that intracellular pH can be measured noninvasively; otherwise it is obscured

Figure 1. ^{31}P spectra of positive response to handgrip stress obtained at 3 tesla (3T) magnet. Rest (left), stress (middle) and recovery (right). During stress, the phosphocreatine level was significantly lowered. PCr: Phosphocreatine.

by overlap of the peaks of 2,3-DPG. A proton decoupler can lead to further improvement in the sensitivity of ³¹P spectroscopy by removing the splitting peak patterns (decoupling) and nuclear Overhauser enhancement [30].

Techniques

Precision and sensitivity of the localization defining the volume of myocardium to be interrogated is crucial to the success of CMR spectroscopy. Contamination from surrounding skeletal muscle, liver or blood pool could significantly compromise the quality of the ³¹P spectra. Depth-resolved surface coil spectroscopy (DRESS) [31], image-selected *in vivo* spectroscopy (ISIS) [32], 1D, 2D and 3D chemical shift imaging (CSI) [33] or a combination of these techniques is generally used. Acquisition weighting is an elaborate technique that improves the spectral quality by reducing contamination from adjacent voxels and by increasing signal-to-noise ratio [34]. It is encouraging that with this technique, the ³¹P signal from inferolateral portions of the left ventricle has sufficient signal-to-noise ratio to allow clinically adequate myocardial evaluation [35]. An excellent approach, spectral localization with optimum pointspread function (SLOOP) [36], that evolved from the spectral localization by imaging (SLIM) [37], allows optimal interrogation from the arbitrary shape of the myocardium. This technique, tailored for each subject, is not yet in general use.

Quantification

Most ³¹P spectra are expressed in relative terms, such as PCr/ATP ratio. This approach may be inadequate when the concentration of the reference metabolites is unstable or both metabolites change in the same direction. Absolute concentration of HEP is of particular importance when measuring reduced ³¹P signals following a myocardial ischemic event, or reduced overall ³¹P metabolite concentration. Absolute quantification can be carried out either by using an

external reference [38] or by using an internal metabolite concentration with less precision [17,39]. SLOOP can be used for this purpose with its inherent absolute quantification characteristics as reported previously [40,41].

Conclusion

The ³¹P CMR spectroscopy provides unparalleled, noninvasive access to the key components of myocardial energy metabolism. Such spectroscopy has been used for uniquely identifying a number of clinically important myocardial disorders. Despite many advantages of the ³¹P CMR spectroscopy, it has not yet become mainstream procedure in clinical practice. The technical feasibility has been documented and the information provides important insight not available with any other noninvasive approaches. However, improvements are needed in order to enhance the diagnostic accuracy. It should be noted that the quality of the ³¹P CMR spectroscopy is highly dependent on the skill of the CMR spectroscopist. At present, we generate diagnostic quality ³¹P spectra in 80% of the patient studies at 3T. We predict that this methodology will gain popularity with continued improvement in technology and education of the clinical cardiovascular specialist. Once these issues are addressed, the ³¹P CMR spectroscopy will be adopted into clinical practice.

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