

# Principals and clinical applications of magnetic resonance cardiac spectroscopy in heart failure

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**Abstract** Cardiac magnetic resonance spectroscopy (MRS) is a noninvasive method to assess by-products of myocardial metabolism. Recent developments in shorter scan protocols and more powerful field strengths have created interest in utilizing this technology in studying and characterizing the metabolic derangements in heart failure patients. Our lack of understanding in heart failure could be greatly enhanced by identifying the metabolic changes and eventually modifying metabolic substrate to achieve improved cardiac mechanics with the aid of this technology. However, there are several impediments for the widespread applicability of this technology. This review discusses the principals of human cardiac MRS and literature pertaining to use of MRS in patients with cardiomyopathy.

**Keywords** Heart Failure · Cardiomyopathy · Magnetic resonance spectroscopy · Review · Metabolic disease

## Introduction

Magnetic resonance cardiac spectroscopy (MRS) has recently emerged as a novel tool that can be used to noninvasively study the metabolism of myocardium. Conceptually, it is similar to other spectroscopic methods that are used to either determine the molecular structure of compounds or the presence of a compound in a

well-defined sample. Another advantage of this method is to the acquisition of the data can be performed repetitively without destroying the sample. In a nutshell, it is based on the phenomenon that certain atoms have a magnetic moment. Nuclei with an odd number of protons and neutrons such as  $^1\text{H}$ ,  $^{31}\text{P}$ ,  $^{13}\text{C}$ ,  $^{23}\text{Na}$ , and  $^{87}\text{Rb}$  have a magnetic moment. These are involved in high-energy phosphate metabolism, Kerb's cycle (tricarboxylic acid cycle), creatine kinase metabolism, and fatty acid metabolism, all of which are essential for viable myocardium. An electromagnetic wave is directed on these molecules that leads to change in magnetic momentum, and hence, energy is released that could be measured and interpreted as a spectrum. Compounds containing these nuclei can be identified and quantified. Compounds such as adenosine triphosphate (ATP) and phosphocreatine (PCr) form the basis of several metabolic processes in myocardium. This was first observed by George Radda using  $^{31}\text{P}$ -MRS while studying skeletal muscles [1]. Later on, Garlick et al. first used it to study isolated perfused heart in 1977 [2]. Since then, this technique has become much advanced. Some of the principals of this technique are given below.

## Principals

While in principal it appears to be a simple procedure however technically it is challenging. This is particularly because heart is constantly in motion and is located behind the chest wall. In addition, the sensitivity of  $^{31}\text{P}$  and  $^{13}\text{C}$  is much lower relative to  $^1\text{H}$  (6.6 and 0.018% of  $^1\text{H}$  sensitivity, respectively) [3]. Therefore, there is low signal to noise ratio, and thus, there is necessity for use of surface coils to enhance the signal. Linearly polarized surface coils used mainly for animal studies become useless in humans and thus the advent of quadrature detection coils are essential. ECG-gating and breath-holding are the other important requirements. In comparison

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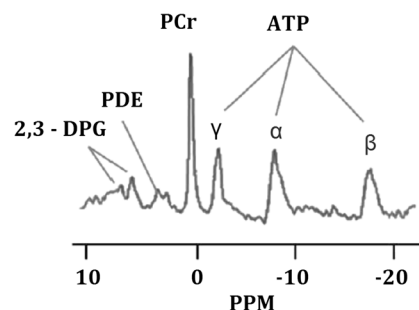
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to  $^{31}\text{P}$ -MRS,  $^1\text{H}$ -MRS does not require special broad band radiofrequency (RF) amplifiers and  $^{31}\text{P}$  tuned RF coils. Therefore,  $^1\text{H}$ -MRS is more widely available. In addition,  $^{31}\text{P}$ -MRS requires some fine tuning to obtain good quality spectra. However, information obtained from  $^1\text{H}$ -MRS differs from the information obtained from  $^{31}\text{P}$ -MRS.  $^{13}\text{C}$ -MRS has limited application in myocardium due to its low sensitivity but potentially can be used to study metabolites of Krebs' cycle, beta oxidation of fatty acids, and pyruvate dehydrogenase flux. The first report of  $^{13}\text{C}$ -MRS in human heart showed its feasibility in four human subjects [4].  $^{23}\text{Na}$ -MRS is also not well established but can be used to investigate and identify myocardial scar. The degree of post infarct scar has shown to correlate with  $^{23}\text{Na}$  signal.  $^{87}\text{Rb}$  is a  $\text{K}^+$  analogue and can help identify function of  $\text{Na}^+/\text{K}^+$  ATPase pump by using  $^{87}\text{Rb}$ -MRS. This review will focus on  $^{31}\text{P}$  and  $^1\text{H}$ -MRS only.

Typically, an MR scout image using spin-echo or single state free precession (SSFP) MR sequence is obtained initially. There are two main methods of localization pulse sequences for  $^1\text{H}$ -MRS. The first, stimulated echo acquisition mode (STEAM) uses three 90 degree pulses and uses TE in the range of 12–20 ms and the second, point resolved spectroscopy (PRESS) uses two slice selective spin-echo sequence and a slice selective excitation pulse to define the volume and uses TE in the range of 25–35 ms. These have been described in more detail elsewhere [5, 6]. Other sequences include depth-resolved surface coil spectroscopy (DRESS), image-selected in vivo spectroscopy (ISIS), and three-dimensional chemical shift imaging (3D-CSI). Signals obtained are corrected for T2 relaxation. End-systolic images using ECG-gating and breath-hold or end expiratory phase using respiratory gating are utilized to obtain good quality spectra. A small volume is selected in the interventricular septum, since it is free of pericardial fat. The volume is typically placed using four-chamber and four short axis images. To ensure that the volume stays on the septum, cine images are used to determine the delay time. Once the spectra are obtained, using a priori spectroscopic knowledge and signal modeling, signals are quantified. Since with  $^{31}\text{P}$ -MRS absolute values of ATP and PCr are difficult to obtain, so only PCr to ATP ratio is usually reported. Normal PCr-to-ATP ratios of healthy subjects range between 1.1 and 2.5.  $^1\text{H}$ -MRS can measure creatine as well as triglyceride content. The triglyceride content is usually expressed in ratio of triglyceride to water (%). Normal ratio is <0.9%. The dominant water related signal and blood contamination are suppressed by using correction factors in order to obtain reliable spectra. Prone position of subjects is favored to minimize the distance between the surface coil and myocardium however studies have studied patients in supine position as well.

Once spectra are obtained, it is essential to follow a standardized data processing methodology. A typical  $^{31}\text{P}$  spectrum from a healthy subject shows six resonances (Fig. 1): 3  $^{31}\text{P}$  atoms ( $\alpha$ ,  $\beta$ , and  $\gamma$ ) of ATP, PCr, 2,3-diphosphoglycerate

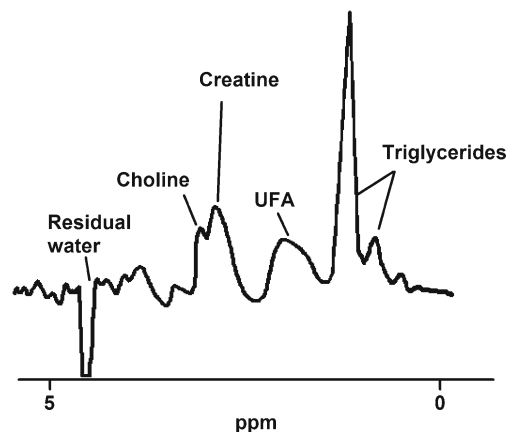


**Fig. 1** A typical  $^{31}\text{P}$ -magnetic resonance spectroscopy spectrum showing 2,3-diphosphoglycerate (2,3-DGP), phosphodiester (PDE), phosphocreatine (PCr), and the three phosphorus peaks of ATP ( $\gamma$ ,  $\alpha$ , and  $\beta$ ). The x-axis is expressed in parts per million (ppm)

(from erythrocytes), and phosphodiesters (from membrane and serum phospholipids). A typical  $^1\text{H}$  spectrum from a healthy subject shows a tall tissue water peak around 5 ppm, a prominent triglyceride peak (composed of methylenes;  $-\text{CH}_2$  and  $-\text{CH}_3$  of fatty acids) and several other peaks of  $^1\text{H}$  rich metabolites (creatine, lactate, choline, and taurine). The first peak is of triglyceride (methylenes of fatty acids) which usually ranges from 1.0 to 2.0 ppm (Fig. 2) Spectra are processed using various softwares, e.g., NUTS software (Acorn NMR, Fremont, Calif) [7], java Magnetic Resonance User Interface (jMRUI) [8] and Advanced Method for Accurate, Robust and Efficient Spectral fitting of MRS data (AMARES) [9]. In summary, there are many phases of MRS that require a certain level of mastery to collect and optimize data signals since it is not an automated process. Consistence of user methods is probably more important than individualizing the settings for obtaining MRS data. A brief review of MRS use in myocardial diseases is discussed below.

## MR spectroscopy and myocardial diseases

MRS use in myocardial disease started to gain momentum in 1990s in the early era of modern revascularization and risk stratification. Initially, in vivo correlation of myocardial



**Fig. 2** A typical  $^1\text{H}$ -magnetic resonance spectroscopy spectrum

metabolism and perfusion was studied [10]. Later on, MRS helped in providing insight into metabolic response of inotropic myocardial stress [11]. A decrease in PCr/ATP ratio or increase in triglyceride to water ratio provided information of myocardial metabolic health. In healthy athlete volunteers, under normal and supranormal cardiac stimulation, the PCr/ATP ratio remained constant. It was not until under extreme inotropic stimulation that PCr/ATP started dropping [12]. Therefore, researchers thought of this as a direct measurement of myocardial bioenergetics and an era of human research experiments began. Table 1 shows the potential changes in metabolites as detected by MRS techniques in various cardiomyopathies. A schematic diagram of myocardial energy metabolism and various metabolites that can be detected by  $^1\text{H}$ ,  $^{31}\text{P}$ , and  $^{13}\text{C}$  MRS techniques is shown in Fig. 3.

### Ischemic heart disease

With ischemia PCr levels drop within seconds of decrease in perfusion [13]. For the preservation of myocardial function, maintenance of high levels of high energy phosphates is required. Decrease in PCr/ATP ratio with isometric exercise (>30% increase in work load) in coronary artery disease (CAD) patients was observed in a study of 16 patients with CAD [14]. This was not observed in normal controls ( $N = 11$ ) and nonischemic patients ( $N = 9$ ). The levels of PCr/ATP returned to normal after revascularization. These findings were further confirmed by other studies with longer follow-ups that studied  $^{31}\text{P}$ -MRS stress test and its prognostic value [15, 16]. However, despite its value as a biomarker test, the lack of spatial and temporal resolution led to its poor clinical acceptance. It cannot identify coronary artery territory better than other much cheaper and less labor-intensive stress tests. A potential role of  $^{31}\text{P}$ -MRS to identify viable myocardium was investigated and showed promise [17]. In hibernating or stunned myocardium, the ATP levels remain near normal

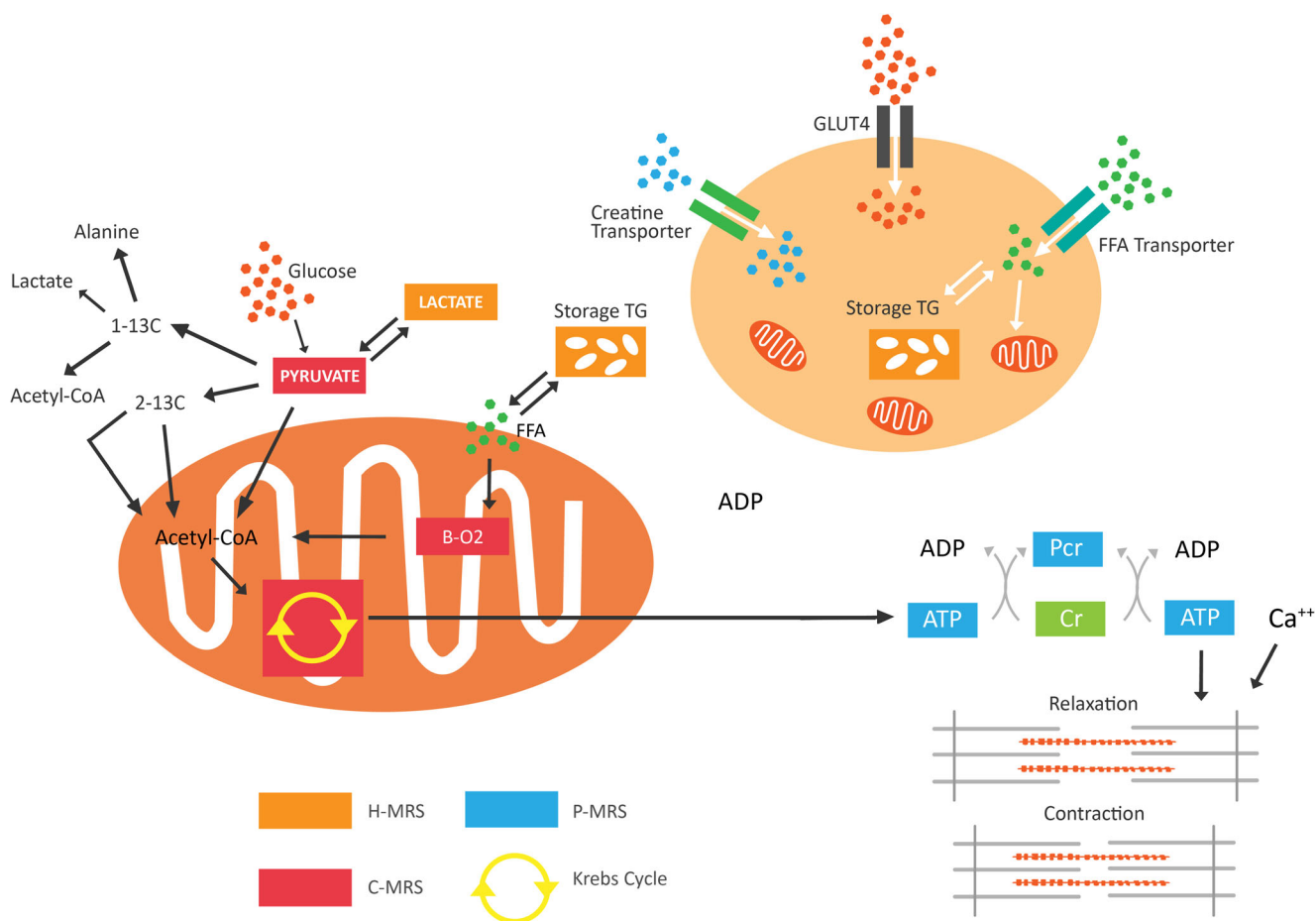
while PCr decrease. On the other hand, in the scarred myocardium both PCr and ATP decrease, so the ratio remained near normal. Due to large variation in the normal values of PCr/ATP, this also remained an unattractive use of  $^{31}\text{P}$ -MRS. In addition, the abnormalities of PCr/ATP are not specific for ischemic damage or nonviability. The approaches used in the prior studies only involved left anterior wall and apex so the inferior and posterior walls cannot be studied. A potential solution is to use higher field strength as 4.1 T has shown to improve voxel size to ~8 ml with much improved spatial resolution [18].

Due to higher sensitivity of  $^1\text{H}$  compared with  $^{31}\text{P}$ ,  $^1\text{H}$  has been studied to examine and shown promise in identifying nonviable myocardium by showing regional creatine depletion [19]. In patients with dilated cardiomyopathy secondary to ischemic heart disease, average PCr/ATP ratio was  $1.53 \pm 0.07$  which was significantly lower than healthy normals  $1.80 \pm 0.06$  [20]. However, the average PCr/ATP ratio of patients with ischemic cardiomyopathy was not different from average PCr/ATP ratio of patients with idiopathic cardiomyopathy and thus questioned the specificity of these ratios for ischemic cardiomyopathy. Similar to infarcted myocardium where PCr/ATP ratio is not useful as both absolute values of PCr and ATP are low, the absolute levels of PCr and ATP in patients with systolic dysfunction and may underestimate the bioenergetics in failing myocardium. Alteration in the preference of glucose versus free fatty acid utilization is controversial and may be studied using methods to assess TCA cycle in conjunction with PCr/ATP ratio. However, modification of myocardial substrate utilization is an area of active investigation and therapeutics needed to alter or improve myocardial bioenergetics may utilize MRS as an intermediate outcome to show efficacy. Creatine is also decreased in ischemic cardiomyopathy and  $^1\text{H}$ -MRS is a much more sensitive method to detect the creatine depletion [19, 21]. Lastly, choline has been shown to be associated with presence and severity of CAD [22]. It can be detected by  $^1\text{H}$ -MRS, but literature is limited

**Table 1** Summary of potential metabolite changes in cardiomyopathies detected by various cardiac magnetic resonance spectroscopy techniques

Metabolites		Ischemic cardiomyopathy	Diabetic cardiomyopathy	Metabolic cardiomyopathy	Valvular cardiomyopathy/hypertrophic cardiomyopathy	Dilated cardiomyopathy
$^{31}\text{P}$	ATP	↓	↓	↓	–	↓
	PCr	↓↓	↓↓	↓↓	–	↓↓
	PCr/ATP	↓	↓	↓	↓	↓
$^1\text{H}$	Triglycerides	↔ or ↑	↑↑	↑↑	–	–
	Creatine	↓↓	↓	↓	↓	↓↓
	Deoxyhemoglobin	↔ or ↑	↔	–	–	–
$^{13}\text{C}$	Alanine	–	–	–	–	–
	Lactate	↑	↔	↔	–	–
	Pyruvate dehydrogenase	↓↓	↓	↓	–	–

PCr phosphocreatine, ATP adenosine triphosphate



**Fig. 3** Schematic representation of myocardiocyte metabolism and application of magnetic resonance spectroscopy techniques

regarding its role in myocardial metabolism. MRS has an edge over the other noninvasive testing modalities as it does not require injection of any contrast agent or radiation and has validated data available regarding its utility in providing information for ischemia and viability in ischemic heart disease. However, due to the large voxel size and poor spatial resolution its progress is impeded until a later day when this issue could be resolved.

**Nonischemic heart disease**

There are two questions that are still unanswered: (1) are changes in myocardial bioenergetics in ischemic and nonischemic myocardium similar or different; (2) do the metabolic changes occur as a bystander or are causal in nature. Even though these have not been definitively answered in literature, there is evidence that these changes differ between ischemic and nonischemic myocardium. Also, diabetic patients have shown to have increased triglyceride content that precedes the symptoms of heart. These findings may suggest that metabolic derangements may be causal in nature. Furthermore, reversal of intramyocardial fat with bariatric

surgery in severe obese individuals improves cardiomyopathy and cardiac mechanics as well as metabolic peaks, suggesting a possible causal relationship. We have classified nonischemic heart disease into (a) metabolic heart disease, (b) valvular heart disease, and (c) inherited cardiomyopathies, and a brief discussion of MRS is included below:

**A. Metabolic heart disease**

Metabolic heart disease is a heterogenous term, but understandably, MRS will have high yield in this group of myocardial diseases. Changes in myocardium of diabetics could be detected as early as 1 year after onset of diabetes [23]. Intramyocardial triglyceride accumulation (cardiac steatosis) is common among patients with diabetes type I and type II [24–27]. The reversal of cardiac steatosis has been observed with caloric restriction [28, 29]. A study that used pioglitazone showed improvement in diastolic function and myocardial glucose uptake without affecting the myocardial triglyceride content, suggesting some signal that it might be of use among patients with diabetic cardiomyopathy [30]. Unfortunately, pioglitazone has a US black box warning regarding its use in heart failure patients and may lead to heart failure in up to 8%

of the patients due to unknown reasons. Patients with dilated cardiomyopathy have 51% lower absolute levels of PCr, 35% lower absolute levels of ATP, and 25% lower levels of PCr/ATP ratio [31]. This has been shown by using spectral localization with optimum point spread function (SLOOP)  $^{31}\text{P}$ -MRS technique that can measure absolute levels of PCr and ATP [31]. Whether lower levels of PCr and ATP precede contractile dysfunction in diabetic cardiomyopathy or are just a compensatory mechanism remains unclear. To answer this, a longitudinal study of diabetes patients would be required. However, patients without CAD but with diabetes are found to have low PCr/ATP, suggesting that PCr/ATP may occur prior to subclinical or clinical dysfunction [27]. Cardiomyopathy that results due to pressure overload such as hypertension has also lower levels of PCr/ATP. In these patients, diastolic dysfunction correlated with PCr/ATP ratios [32]. Once systolic dysfunction sets in, the PCr/ATP levels further decrease [33]. Dilated cardiomyopathy is usually a final common pathway of most of the metabolic cardiomyopathies. Figure 4 shows the differences in the  $^{31}\text{P}$ -MRS spectra of normal and dilated cardiomyopathy patients.

#### B. Valvular heart disease

Among patients with valvular heart disease, PCr/ATP ratio has shown to be reduced in heart failure patients with mitral regurgitation or aortic stenosis [34–36]. Presence of myocardial hypertrophy was common in these patients. The levels of PCr/ATP ratio improved significantly from  $1.28 \pm 0.17$  to  $1.47 \pm 0.14$ , 9 months after aortic valve surgery [37]. These changes have even been observed in patients with severe aortic stenosis and subclinical left ventricular dysfunction. Both perfusion reserve and oxygenation as measured by blood-oxygen level dependent (BOLD) signal showed improvement in left ventricular strain and energetics 8 months after aortic valve replacement [38]. With the advent of transcatheter therapies, it would be interesting to study bioenergetics after transcatheter aortic valve implantation. Currently, the timing for valve surgery is based on echocardiographic measures. It might be possible that in the future, measurements of cellular level biomolecular changes could guide these valvular

replacement procedures before the development of ventricular dysfunction.

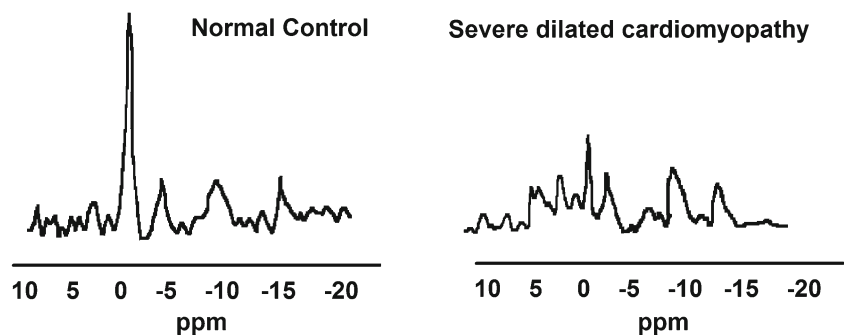
#### C. Inherited cardiomyopathies

Symptomatic and asymptomatic patients with hypertrophic cardiomyopathy have shown to have decreased PCr/ATP ratio [39–41]. This is also shown in hypertrophic cardiomyopathy of genetic origin [40, 42, 43]. This preexisting energy deficit is exacerbated with exercise stress as measured by  $^{31}\text{P}$ -MRS [44]. This might explain the exercise-induced diastolic dysfunction in these patients. Female carriers and patients of Becker's muscular dystrophy also have low levels of PCr and ATP when compared with normal volunteers [45]. Patients with familial hypercholesterolemia [46] and hemochromatosis [47] also have low levels of PCr/ATP ratio. Statins have shown to improve PCr/ATP ratio in familial hypercholesterolemia [46]. Myocardial fat depots in Anderson-Fabry's disease, an inherited X-linked lysosomal storage disease could be studied using  $^1\text{H}$ -MRS [48]. This study observed that in advanced Fabry's disease, the triglyceride content was found to be severely elevated. This suggests a possible role in monitoring progression of disease in these patients.

### Cardiac transplant

$^{31}\text{P}$ -MRS can detect post-transplant acute rejection by showing low PCr/ATP ratio. The ratio of PCr/ATP is lower early post-transplant but improves with time. However, these ratios did not correlate with the cardiac biopsy findings. Another study evaluated  $^{31}\text{P}$ -MRS stress test and showed that 40% of the transplant recipients had >25% decrease in PCr/ATP ratio. The significance of this finding is not clear. Early noninvasive detection of transplant rejection could become an important discovery and could help target immunosuppressive therapy. Use of  $^{13}\text{C}$ -hyperpolarized MRS might help unravel many of the myocardial changes that occur with immunosuppressive therapy and could lead to chronic allograft vasculopathy and rejection.

**Fig. 4**  $^{31}\text{P}$ -magnetic resonance spectroscopy spectral differences between normal and dilated cardiomyopathy patient



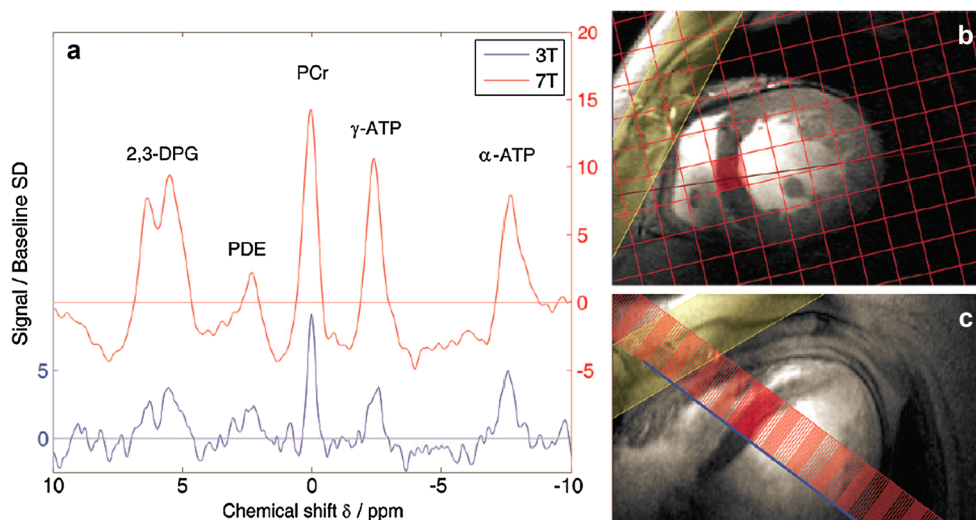
## Response to heart failure treatment

Patients treated with diuretics, beta-blockers, and angiotensin-converting enzyme inhibitors showed an improvement in PCr/ATP ratio from  $1.51 \pm 0.32$  to  $2.15 \pm 0.27$  within 3 months of therapy that paralleled the clinical improvement [49]. Myocardial substrate modifiers such as trimetazidine have also been examined. Trimetazidine inhibits fatty acid oxidation and switches myocardial metabolism to glycolysis. There was improvement in PCr/ATP ratio by 33% in trimetazidine-treated patients compared to placebo ( $1.35 \pm 0.33$  vs.  $1.80 \pm 0.50$ , respectively) [50]. Another trial studying the effect of supervised exercise training in patients with dilated cardiomyopathy observed that PCr/ATP levels did not change, but there was an improvement in LV function, suggesting that exercise does not adversely affect the myocardial metabolism. Such designs can be used to assess therapies in clinical heart failure trials [51]. More recently, beta-blocker use in heart failure showed favorable cardiac energetics. [52] In a study of patients with dilated cardiomyopathy, treatment with recombinant human growth hormone led to increase in PCr/ATP ratio and myocardial mass. However, improvement in myocardial function was not demonstrated [53]. More recently, using a combination of  $^1\text{H}$ -MRS,  $^{31}\text{P}$ -MRS, and MR imaging, researchers showed that short-term caloric restriction led to increase in myocardial triglyceride levels without affecting PCr/ATP ratio [54]. Another dietary study of high-fat diet in 16 volunteers showed impaired PCr/ATP ratios without altering cardiac function [55]. These studies suggest that dietary interventions and their effects on myocardium can be studied by using MRS. Despite MRS showing promise in determining the effects of some of the heart failure therapies,

more work is still needed to define MRS role in monitoring and determining the effect of these therapies. A possible use of MRS to show improvement or reversal of diabetic cardiomyopathy after the use of advanced glycation end-product inhibitor could be its important contribution to the field of science.

## Future directions

Even though the field has existed for >3 decades, the penetration of this technology into clinical realm is still not fully realized. The future awaits the technological advances with increase in magnetic field signal strength to a level where spatial and temporal resolutions become meaningful. Three tesla is better than 1.5 T, and 7 T is better than 3 T [56, 57]. Seven tesla can provide a resolution of <5 ml. A comparison of spectra obtained at 3 and 7 T is given in Fig. 5. Scan timings have been decreasing, and it has been shown that ~1.5 min  $^1\text{H}$ -MRS scan can provide reliable information about triglycerides, creatine, and choline myocardial content [58]. However, spectral separation of creatine and choline spectral peaks at 3.0 and 3.2 ppm is reduced when fewer  $^1\text{H}$ -MRS signals are averaged in a shorter period of acquisition. Regional temporal changes in biochemical processes in real time have not been well studied, but with enhanced temporal resolution, it could become one of the possibilities. In addition to field strength, advanced coil design and sequence development might enhance the quality of spectral signals and provide more granular data regarding the metabolites. The reproducibility of signals is another hurdle which also needs to be addressed by using well-defined protocols. Part of this is due to poor signal to noise ratio, which can be boosted by using



**Fig. 5** **a** Graph shows comparison of spectra in a typical patient (57-year-old woman) at 3 and 7 T. These spectra have had a matched filter applied and have been normalized to mean baseline noise, so the PCr peak height is, by definition, the PCr SNR. Increase in SNR at 7 T is readily apparent. **b** Corresponding mid-short axis localizer image acquired at 7 T. **c**

Corresponding four-chamber localizer image acquired at 7 T. The spectroscopy matrix is overlaid in red, and the voxel plotted in **a** is highlighted. The yellow-shaded region denotes the regional saturation slab used to suppress signal from overlying skeletal muscle

dynamic nuclear hyperpolarization. Direct estimation of myocardial TCA flux in vivo has been demonstrated using hyperpolarized  $^{13}\text{C}$ -MRS [59]. This field is rapidly expanding with several experiences noted in the literature [60, 61].

## Conclusions

In conclusion, MRS is still limited to research settings where it provides noninvasive fundamental insight into myocardial metabolism. Technical advances in developing techniques to enhance spatial and temporal resolution will dramatically expand its application to clinical realm. Since the epidemiology of cardiac diseases is changing, with disproportionate increase in metabolic diseases when compared with ischemic heart disease, the utility of MRS will expand. Future studies should focus on designing larger cohort studies that employ MRS to study the fundamental changes in cardiac metabolism.

## Compliance with ethical standards

**Conflicts of interest** Dr. Qureshi reports receiving honorarium/consultation fee from Medicare.

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