Ischemic Heart Disease and Heart Failure: Advanced Magnetic Resonance Spectroscopy and Metabolic Imaging

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Ischemic heart disease and heart failure are common cardiac disorders. Magnetic resonance spectroscopy (MRS) is a non-invasive diagnostic tool for biochemical characterization of normal and abnormal tissues in the heart that has advantages over other diagnostic methods for quantification of myocardial metabolism without the use of contrast agents or invasive radiation. ¹H MRS and ³¹P MRS are mainly used in clinical and preclinical research to monitor metabolic changes in the myocardium, providing valuable information on metabolite-based diagnostic and therapeutic outcomes. This review discusses the potential diagnostic biomarkers for ischemic heart disease and heart failure in multinuclear MRS and metabolic imaging. In addition, the future directions of MRS including hyperpolarized ¹³C MRS and high-field-strength MRS techniques, which are useful for early diagnosis and prediction of therapeutic response in heart diseases, are briefly reviewed.

Key words Heart · Heart failure · Ischemic heart disease ·
 Magnetic resonance spectroscopy · Metabolism.

INTRODUCTION

Cardiovascular disease refers to several conditions of the heart and blood vessels, including ischemic heart disease (coronary heart disease), heart failure, cerebrovascular disease, elevated blood pressure, peripheral artery disease, rheumatic heart disease, and congenital heart disease. Ischemic heart disease is the principal etiology of heart failure; in particular, myocardial ischemia plays an important role in cardiac remodeling, a process that leads to progressive change in the shape and size of the heart and significantly worsens the prognosis of patients with heart failure [1].

Ischemic heart disease and heart failure lead to left ventricular (LV) dysfunction including systolic and diastolic dysfunction, which have been shown to have poor prognosis with high mortality at the last stage, and sudden cardiac death [2]. Ischemic heart disease and heart failure are common cardiac disorders in the United States, accounting for up to 45.1% and 8.5%

of all cardiac deaths in 2014, respectively [3]. Early diagnosis is essential to prevent the progression of these diseases.

The heart has a very high and continuous demand for energy production in the form of adenosine triphosphate (ATP) [4,5]. Under normoxic conditions, more than 95% of the ATP generated in the heart is derived from oxidative phosphorylation in the mitochondria. The remaining 5% comes mainly from glycolysis and to a lesser extent from the Krebs cycle [6]. Fatty acids enter the mitochondria, where β -oxidation takes place, after which the intermediate acetyl-coenzyme A enters the Krebs cycle [7]. Glucose is converted to pyruvate in the cytoplasm by glycolysis, and then the pyruvate enters the Krebs cycle in the mitochondria [7]. In addition, ATP is synthesized in the mitochondria and reacts with creatine (Cr) in the creatine kinase (CK) reaction to form phosphocreatine (PCr) as follows [8]: $ATP + Cr \leftrightarrow ADP + PCr + H^+$.

Coronary angiography is recognized as the gold standard for diagnosis of ischemic heart disease, whereas echocardiography is the gold standard for assessment of LV systolic dysfunction and detection of systolic heart failure [9,10]. MRI is a noninvasive modality that has been used to assess cardiac morphology,

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function, perfusion, and viability. Moreover, echocardiography is the most useful noninvasive imaging modality in the diagnosis of heart failure. Unlike MRI and echocardiography, magnetic resonance spectroscopy (MRS) allows investigation of intracranial cellular metabolism *in vivo*. Under the assumption that metabolite changes in abnormal tissue precede morphological changes, the magnetic resonance spectra represent specific biochemical information about metabolic changes at the cellular level and can support the clinical diagnosis because they provide information on the biochemistry and physiology of the corresponding disease [11,12]. Thus, MRS has become a tool of interest for diagnostic and prognostic assessment of ischemic heart disease and heart failure.

In vivo MRS plays an important role in early diagnosis and evaluation of effective therapeutic intervention in myocardial muscles. ^1H and ^{31}P MRS have predominantly been used to distinguish between non-viable and viable myocardium and to diagnose heart failure [13-17]. Moreover, with the advent of the 7-tesla (T) MRI system, spectral resolutions are enhanced even further compared with the 1.5 T and 3 T systems, providing more accurate quantification of cardiac metabolites. Recently, hyperpolarized ^{13}C MRS and metabolic imaging have opened new possibilities for assessing diagnostic and therapeutic biomarkers of cellular metabolic changes in heart diseases in both clinical and preclinical research [18-22]. This brief review discusses potential diagnostic biomarkers for ischemic heart disease and heart failure and further introduces the future directions of MRS including hyperpolarized ^{13}C MRS and high-field-strength MRS techniques.

CARDIAC MAGNETIC RESONANCE SPECTROSCOPY

Metabolism is an essential process for maintaining living cells, which are the fundamental units of all living tissues. Cardiac MRS is a noninvasive technique for biochemical characterization of normal and abnormal tissues of the heart and has been used to assess myocardial metabolism using the signals from nuclei, such as ^1H (hydrogen (^1H), ^{13}C (carbon (^{13}C), ^{23}Na (sodium (^{23}Na), and ^{31}P (phosphorus (^{31}P)).

^1H MRS has been applied to the heart because of its major advantages of higher sensitivity and spatial resolution [23]. This technique can identify hypertrophy of a remodeled myocardium but does not discriminate between nonviable and viable tissue [24]. It is widely recognized that the important ^1H metabolites in the myocardium are lipids (triglycerides) and Cr. Myocardial infarction is associated with increased myocardial lipid content and decreased myocardial Cr content. The chemical shifts of ^1H metabolites in ^1H MRS are typically observed in the range of 0.0 to 9.0 ppm, whereas those of ^{31}P metabolites in

^{31}P MRS are widely observed in the range of 40 ppm. ^{31}P MRS allows detection of a wider range of cardiac metabolites compared with ^1H MRS but has lower sensitivity. ^{31}P metabolites are abundant in viable tissues and play an important role as high-energy compounds that are regulated in intracellular metabolism. ^{31}P MRS is widely used for noninvasive measurement of intracellular pH and Mg^{2+} levels by utilizing the changes in chemical shifts between PCr and inorganic phosphate (Pi) and between $\alpha\text{-ATP}$ and $\beta\text{-ATP}$ [25]. Most ^{31}P MRS studies demonstrated that the PCr/ATP ratio is an index of the energetic state of the heart. PCr is an important short-term reserve energy source that maintains a high phosphorylation potential under conditions of increased energy demand, such as during exercise and ischemia [26]. ATP is the direct energy source for energy-consuming reactions in the cell, whereas PCr acts as an energy storage compound and as an energy transport molecule in the CK-PCr energy shuttle [27]. Especially, a decreased myocardial PCr/ATP ratio is linked to increased mortality in patients with heart failure [28].

Beyond ^1H and ^{31}P , ^{13}C MRS is a useful tool for evaluating the kinetics of metabolism. ^{13}C MRS is an important modality capable of evaluating the kinetics of cardiac metabolism. Its sensitivity is very low because of its low natural abundance, even with exogenously introduced isotopic enrichment [29]. Advances in ^{13}C hyperpolarization, such as dissolution dynamic nuclear polarization (DNP), enhance the spectral sensitivity more than 10000 times compared with conventional ^{13}C MRS [30-33]. This technique allows quantification of metabolic reactions such as Krebs cycle flux and various metabolic pathways [16]. ^{13}C -labeled pyruvate is a commonly used substrate for obtaining important information on the biochemical pathway as it can be converted to [$1\text{-}^{13}\text{C}$] lactate, [$1\text{-}^{13}\text{C}$] alanine, and [^{13}C] bicarbonate and has been proposed as a cardioprotective agent during ischemic conditions [24,29,34]. Therefore, ^{13}C holds great potential for studying multiple metabolic pathways such as glycolysis, the tricarboxylic acid cycle, or β -oxidation in the myocardium [35].

ISCHEMIC HEART DISEASE

Ischemic heart disease is characterized by reduced blood flow and oxygen to the cardiac muscles, leading to regional ischemia and infarction. The main clinical issue in the treatment of patients with ischemic heart disease is identification of viable myocardium and its discrimination from non-viable necrotic tissue [36]. MRS is a potential diagnostic tool for distinguishing between nonviable and viable myocardium and has advantages over other diagnostic tools in the ability to determine myocardial viability without the use of contrast agents or invasive radiation [16].

In general, ^{31}P MRS is mainly used in clinical fields to assess cardiac metabolism in ischemic heart disease. In patients with 70% or greater stenosis of the left anterior descending coronary artery, the PCr/ATP ratio decreased from 1.45 ± 0.31 at rest to 0.91 ± 0.24 during hand-grip exercise and increased to 1.27 ± 0.38 after recovery [17]. After revascularization, the PCr/ATP ratio was stable during the repeated exercise. In another study [15], the PCr/ATP ratio decreased by 25% during hand-grip exercise in 7 of 35 women with chest pain and normal coronary angiograph, suggesting microvascular coronary artery disease as the cause of the chest pain and consistent with the occurrence of myocardial ischemia. Interestingly, a 3-year follow-up study [37] on the prognostic implications of abnormal PCr/ATP ratio was performed in women with chest pain and normal coronary angiography, with or without an abnormal PCr/ATP ratio, and a reference group with coronary artery disease. The results demonstrated that a decrease in PCr/ATP of 1% increased the risk of a cardiovascular event by 4% after adjusting for coronary artery disease and cardiac risk factors, suggesting that the ^{31}P -MRS stress test is a strong predictor of future cardiovascular events.

Similar to ischemic tissue, the PCr/ATP ratio in the infarcted region of patients with aortic stenosis (pressure gradient >60 mm Hg) decreased compared with that in healthy controls [38]. After surgical valve replacement, the PCr/ATP ratio in patients increased from 0.80 ± 0.25 to 1.28 ± 0.22 , and changes in cardiac energy metabolism showed a trend toward normalization. In addition, ATP content is used in clinical fields to evaluate myocardial viability. A human study by Yabe et al. [39] demonstrated that PCr and ATP contents decreased significantly in patients with both reversible and fixed ^{201}Tl defects, whereas ATP content only decreased in patients with fixed thallium defects. In nonviable infarcted canine myocardium, the PCr/ATP ratio, PCr, and ATP were significantly decreased, and these alterations were confirmed using biopsy measurements [14]. In isolated rat hearts after 10-min coronary artery occlusion and 15-min reperfusion, the PCr level rapidly decreased at the onset of ischemia and rapidly recovered to the preischemic level after reperfusion (Fig. 1) [40]. However, in rat hearts, the PCr/ATP ratio could not be used to assess myocardial viability because PCr and ATP signals cannot be detected in the infarcted region [41].

In a human study using ^1H MRS, Bottomley and Weiss [13] demonstrated that Cr content was significantly lower in infarcted myocardium compared with viable myocardium. Patients with hypokinetic wall motion and those with akinetic or dyskinetic wall motion showed decreased Cr peaks compared with patients with normokinetic LV wall motion and normal controls (Fig. 2) [42]. Numerous ^1H MRS studies [14,43–45] were performed in animals to distinguish between nonviable

Fig. 1. Time-course changes in ATP, PCr, Pi, and pH before, during, and after ischemia in isolated rat hearts following 10-min coronary artery occlusion and 15-min reperfusion. The ATP level gradually decreased during ischemia and partially recovered to the pre-ischemic level after reperfusion. The PCr level rapidly decreased at the onset of ischemia and rapidly recovered to pre-ischemic level after reperfusion. The Pi level rapidly increased at the onset of ischemia and rapidly decreased to the pre-ischemic level after reperfusion. The pH level gradually decreased during ischemia and rapidly recovered to the pre-ischemic level after reperfusion. Reprinted from Schroeder et al. *Cardiovasc Res* 2010;86:82-91, with permission of Oxford University Press [40]. ATP: adenosine triphosphate, PCr: phosphocreatine, Pi: inorganic phosphate.

and viable myocardium. The Cr content in nonviable infarcted canine myocardium was decreased compared with that in viable myocardium [14]. Myocardial infarction is related to accumulation of lipids. Evanochko et al. [44] investigated lipid content changes in the canine myocardium after 24-h coronary occlusion and reported increased lipid content in myocardia with moderate blood flow reduction (flow 5–50% of control) compared with myocardia with normal blood flow or severe blood flow reduction (flow $<5\%$ of control). In a swine model after 48-min coronary artery occlusion and 2-h reperfusion, the Cr level decreased from 18.28 ± 0.84 $\mu\text{mol/g}$ fresh weight in controls to 12.58 ± 2.89 $\mu\text{mol/g}$ fresh weight ($p < 0.05$) and 9.96 ± 2.21 $\mu\text{mol/g}$ fresh weight ($p < 0.01$) in at-risk and necrotic areas, respectively (Fig. 3) [45]. In addition, high-resolution magic angle spectroscopy spectra showed an increase in lipid signals at 0.9 ppm and 1.28 ppm as markers of necrotic tissue. In a similar

Fig. 2. Myocardial ^1H MR spectra obtained in the left ventricular (LV) wall of patients with ischemic heart disease (A–C) and a healthy control (D). Patients in hypokinetic wall motion (WH) and akinetic or dyskinetic wall motion (WA) showed decreased creatine peaks compared with patients in normokinetic LV wall motion (WN) and healthy controls (HC). Reprinted from Nakae et al. *J Cardiovasc Magn Reson* 2004;6:685–696 [42].

study [43], lipid content increased in the regions corresponding to myocardial infarction, particularly in the periphery of the infarction. ^1H MRS is a valuable diagnostic tool capable of differentiating normal, at-risk, and infarcted myocardium.

During the last two decades, ^{13}C and ^{23}Na MRS have been performed to identify myocardial viability in animals, but not in humans. Horn et al. [46] demonstrated that sodium (^{23}Na) content was increased in non-viable myocardium of rats. Hyperpolarized ^{13}C MRS is used in the preclinical field to assess cardiac metabolism in viable and non-viable myocardium [18,19,47]. Golman et al. [19] investigated myocardial viability in a pig model of ischemia-reperfusion using hyperpolarized ^{13}C MRS and metabolic imaging and reported a decreased level of [^{13}C] bicarbonate in stunned viable myocardium after 15-min coronary occlusion (ischemic) and decreased levels of [^{13}C] bicarbonate and [$1\text{-}^{13}\text{C}$] alanine in non-viable myocardium after 45-min occlusion (infarction) (Fig. 4). In a similar study [47], at reperfusion after 15-min of coronary occlusion, the [$1\text{-}^{13}\text{C}$] lactate/[^{13}C] bicarbonate ratio was increased in the myocardial area in at-risk rats (Fig. 5). The Krebs cycle plays a fundamental role in cardiac energy production. A hyperpolarized ^{13}C MRS study [20] using [$2\text{-}^{13}\text{C}$] pyruvate measured Krebs

Fig. 3. ^1H HR-MAS spectra of control (A), at-risk (B), and necrotic (C) tissue after myocardial infarction in a swine model following 48-min coronary artery occlusion and 2-h reperfusion. Creatine concentration in at-risk (B) and necrotic (C) tissue decreased. Spectra A and B are scaled for a similar tissue mass, and spectrum (C) has a vertical scale with 4-fold enlargement. Reprinted from Barba et al. *MAGMA* 2007;20:265–271, with permission of Springer Nature [45]. Lip 1: CH_3 of lipid chains, Lip 2: $\text{-CH}_2\text{-}$ of lipid chains, Cr: creatine, Gln: glutamine, Tau: taurine, m-Ino: myo-inositol.

cycle flux in real time in perfused rat hearts. The data suggested that the levels of [$1\text{-}^{13}\text{C}$] citrate and [$5\text{-}^{13}\text{C}$] glutamate were decreased after 10-min of global ischemia in an isolated heart, whereas that of lactate was increased. Hyperpolarized ^{13}C MRS allows determination of myocardial viability by evaluating the severity of hypokinetic wall motion.

Major multinuclear MRS techniques including ^1H , ^{31}P , hyperpolarized ^{13}C , and ^{23}Na MRS have the potential to discriminate the viability of ischemic myocardium in preclinical and/or clinical studies. ^1H MRS is ideally suited to assess the metabolism of the infarcted tissue through increased lipid and decreased Cr. The PCr/ATP ratio in cardiac energy metabolism is a potentially important diagnostic biomarker for quantifying cardiac function, especially in ischemic heart disease. Also, hyperpolarized ^{13}C MRS studies [19,47] suggested that an increased ratio of [$1\text{-}^{13}\text{C}$] lactate/[^{13}C] bicarbonate or decreased signals of both [^{13}C] bicarbonate and [$1\text{-}^{13}\text{C}$] alanine predict myocardial infarction. In addition, increased ^{23}Na content could be an indicator of myocardial infarction.

HEART FAILURE

Heart failure is a common final pathway of various cardio-

Fig. 4. Proton MR images with semiquantitative Gd-perfusion and delayed enhancement and metabolic images of $[1-^{13}\text{C}]$ alanine and $[^{13}\text{C}]$ bicarbonate before (A) and after (B, C) occlusion in a pig model. Decreased level of bicarbonate in stunned viable myocardium after 15-min coronary occlusion (B) and decreased levels of bicarbonate and alanine in non-viable myocardium (arrows) after 45-min occlusion (C). Reprinted from Golman et al. Magn Reson Med 2008;59:1005-1013, with permission of John Wiley and Sons [19].

vascular diseases [48]. The most common causes of heart failure are dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), and cardiomyopathy related to metabolic syndrome [7]. DCM is characterized by LV systolic dysfunction with associated increase in mass and volume. HCM is a myocardial disease defined by unexplained LV hypertrophy, usually asymmetrical and involving the interventricular septum [49]. Alterations in cardiac energy metabolism play an important role in the mechanisms of heart failure [50]. Myocardial lipid over-storage leads to cardiomyopathy; however, advanced heart failure causes lipolysis via sympathetic nerve activation [51].

Patients with heart failure with preserved ejection fraction (HFpEF) show decreased PCr/ATP ratio by ^{31}P MRS compared with healthy controls. The PCr/ATP ratio in patients with heart failure treated with trimetazidine increased by 33% from 1.35 ± 0.33 to 1.80 ± 0.50 , resulting in decreased New York Heart Association (NYHA) class and increased ejection fraction [52]. Such evidence suggests that the decreased PCr/ATP ratio was attributable to the pathophysiology of heart failure. Studies [53-55] on higher-energy metabolism using ^{31}P MRS in patients with DCM reported decreased PCr/ATP ratios (Fig. 6). This decrease correlates with the clinical severity of heart failure estimated from the NYHA class [53] and LV ejection fraction [54,55]. Interestingly, the PCr/ATP ratio after drug treatment increased by 42%, from 1.51 ± 0.32 to 2.15 ± 0.27 [53]. However, in patients with

DCM, a ^{31}P MRS study [27] with spatial localization and optimum point-spread function, a new method for absolute quantification of myocardial high-energy phosphate level, reported 51% and 35% reductions in PCr and ATP levels, respectively, resulting in a 25% decrease in PCr/ATP ratio. These results suggest that the PCr/ATP ratio underestimates the true extent of energetic imbalance.

Cardiac ^{31}P MRS has also been used to evaluate disordered energy metabolism and pH value in hypertrophic myocardium [26,55-57]. Patients with HCM showed a decreased PCr/ATP ratio compared with healthy controls (Fig. 7); however, the PCr/ATP ratio was not correlated with degree of LV hypertrophy [57]. In addition, patients with nonobstructive HCM showed a significant increase in myocardial lipids and a decrease in PCr/ γ -ATP ratio compared with competitive athletes [58]. During myocardial ischemia, oxygen consumption and ATP production are reduced, causing accelerated glycolysis and lactate production; in this situation, pH decreases and cell function is impaired [59]. One study [55] reported that the myocardial pH level (7.07 ± 0.07) in patients with HCM was lower than that in healthy controls (7.15 ± 0.03). Patients with type I or type II diabetes showed a decreased PCr/ATP ratio compared with healthy controls [60,61], and the PCr/ATP ratio correlated negatively with fasting plasma free fatty acid concentration [60].

^1H MRS studies [51,62,63] have demonstrated that lipid is

Fig. 5. Example images at the five time points in a rat. (A) Cine images at reperfusion in a rat model show reduced systolic wall thickening in the myocardial area at risk (AAR), which is the myocardial territory distal to the coronary occlusion (anterior and lateral walls) (arrow). (B) Metabolic maps of $[1-^{13}\text{C}]$ lactate, $[^{13}\text{C}]$ bicarbonate, and $[1-^{13}\text{C}]$ lactate/ $[^{13}\text{C}]$ bicarbonate (Lac/Bic) ratio. In the AAR, the Lac/Bic ratio is increased. Hyperpolarized $[1-^{13}\text{C}]$ pyruvate was injected at the following times in the course of reperfusion: 3 min, 30 min, 60 min, and 1 week after 15-min coronary occlusion. Reprinted from Oh-Ici et al. *Radiology* 2016;278:742-751, with permission of Radiological Society of North America [47].

more strongly associated with the specific cause of disease than the severity of cardiac dysfunction, and that Cr reflects the severity of heart failure. Nakae et al. [51] reported that lipid content was significantly lower in patients with HCM than in healthy controls; however, the lack of a significant difference in lipid between patients with DCM and healthy controls suggests that lipid may be related to an overweight state. The Cr level in patients with chronic heart failure (LV ejection fraction <45%) was significantly lower than that in healthy controls [62]. Two studies [51,63] demonstrated that patients with HCM and DCM showed decreased Cr content, which correlated positively with LV ejection fraction. Myocardial energy expenditure is associated with changes in LV ejection fraction. Du et al. [64] revealed that se-

rum metabolomic markers such as 3-hydroxybutyrate, acetone, and succinate were significantly increased in patients with heart failure, and that these changes could be used as potential indicators of heart failure. Myocardial triglyceride content is significantly higher in patients with type II diabetes compared with healthy volunteers [65]. Obesity is also associated with increased myocardial lipidosis [66].

Schroeder et al. [67] investigated the cellular metabolite change in the myocardium of a porcine model using hyperpolarized ^{13}C MRS and suggested that the ratios of $[5-^{13}\text{C}]$ glutamate/ $[1-^{13}\text{C}]$ pyruvate and $[^{13}\text{C}]$ bicarbonate/ $[1-^{13}\text{C}]$ pyruvate significantly decreased with progression of DCM. In hypertrophied hearts, the rate of conversion of pyruvate to lactate is increased

Fig. 6. Myocardial ^{31}P MR spectra from a healthy control (A) and a patient with dilated cardiomyopathy (B). The PCr/ATP ratio in a patient with DCM was significantly lower compared with a healthy control. Reprinted from de Roos et al. *J Magn Reson Imaging* 1992;2:711-719, with permission of John Wiley and Sons [55]. 2,3-DPG: 2,3-diphosphoglycerate, PCr: phosphocreatine, ATP: adenosine triphosphate, DCM: dilated cardiomyopathy, SPL: serum phospholipids.

Fig. 7. Spin-echo MR images (A and C) and ^1H MR spectra from a 66-year-old healthy control (B) and a 79-year-old patient with hypertrophic cardiomyopathy (HCM) (D). The creatine concentrations in the healthy control and patient were 25.0 and 15.6 $\mu\text{mol/g}$ wet weight, respectively. Reprinted from Nakae et al. *J Am Coll Cardiol* 2003;42:1587-1593, with permission of Elsevier Science and Technology Journals [63].

[68]. Further studies using hyperpolarized ^{13}C metabolic imaging would be useful to assess diagnosis and therapeutic evaluation in heart failure, providing more accurate metabolic mapping.

Although both PCr and ATP contents decrease in heart failure, the PCr/ATP ratio correlates with clinical severity of heart failure. ^1H MRS has demonstrated decreased lipid content in HCM and decreased lipid and Cr contents in both HCM and DCM. These cardiac metabolites could be reliable predictors of heart failure. Very few clinical MRS studies have focused on heart failure; thus, future studies combining ^1H , ^{13}C , and ^{31}P MRS techniques are needed.

FUTURE DIRECTIONS

Today, the most frequently used magnetic resonance scan-

ners for cardiac MRS operate at 1.5 T and 3 T. However, clinical application of ^1H and ^{31}P MRS is limited by the many unresolved problems related to heavy spectral overlap. The application of a higher magnetic field is a good solution to reduce the limitations of *in vivo* cardiac MRS studies. A higher field strength provides accurate and reliable interpretation of the magnetic resonance spectra. For example, the spectral signal-to-noise ratio at 3 T is about two times higher than that at 1.5 T [69]. With an increase in magnetic field strength, the signal-to-noise ratio and temporal resolution also increase. However, higher field strengths are also associated with magnetic field inhomogeneities, motion-induced artifacts, increased chemical shift displacement errors, and higher specific absorption rate. Some of these issues are inherent physical properties of the biochemical component under investigation, whereas others may be addressed by improving the technology, either in pulse sequence design or

Fig. 8. Comparison of MR spectra in a 57-year-old woman with dilated cardiomyopathy (DCM) at 3 T and 7 T (A). The increase in SNR at 7 T is readily apparent. Corresponding mid-short axis view (B) and four-chamber view (C) were acquired at 7 T. The spectroscopy matrices are overlaid in the red voxels plotted in B and C is highlighted. The yellow-shaded region denotes the regional saturation slab used to suppress signal from overlying skeletal muscle. Reprinted from Valkovič et al. *Magn Reson Med* 2017;78:1667-1673, with permission of Radiological Society of North America [73]. 2,3-DPG: 2,3-diphosphoglycerate, PDE: phosphodiester, PCr: phosphocreatine, ATP: adenosine triphosphate.

Fig. 9. ^{13}C MR images displayed as color overlays on top of grayscale anatomic images in mid-left ventricle (LV) slices from a healthy subject (A-C). A representative ^{13}C spectrum acquired using a nonselective excitation pulse is illustrated (D), and the ratios of $[1-^{13}\text{C}]$ lactate/ $[1-^{13}\text{C}]$ pyruvate and $[^{13}\text{C}]$ bicarbonate/ $[1-^{13}\text{C}]$ pyruvate in three healthy subjects are shown in (E) and (F), respectively. Reprinted from Cunningham et al. *Circ Res* 2016;119:1177-1182, with permission of Wolters Kluwer Health [21].

Fig. 10. Intracellular pH measurements using the ratio between HCO_3^- and CO_2 at equilibrium state on a mid-ventricular slice of rodent heart. The scale bar indicates 1 cm. The pH level was measured as 7.15 ± 0.04 at baseline (A) and decreased to 6.90 ± 0.06 following 15 min of continuous β -adrenergic stimulation (B). Reprinted from Lau et al. Magn Reson Med 2017;77:1810-1817 [79].

scanner hardware [70].

Several ^{31}P MRS studies [71-73] were performed using a 7 T MRI unit, which can more precisely quantify the spectral information than a 3 T unit. It is well known that mean Cramer Rao lower bound indicates spectral fitting uncertainty, and values of PCr and PCr/ATP at 7 T are 2.4 times and 2.7 times lower than those of 1.5 T, respectively, resulting in enhanced spectral quantification accuracy at a higher field [71]. In a clinical study [74] using 7 T, patients with DCM had a significantly lower PCr/ATP ratio than healthy controls (1.54 ± 0.39 vs. 1.95 ± 0.25 , $p = 0.005$), which is consistent with previous findings at lower field strengths (Fig. 8). A hyperpolarized ^{13}C MRS study [75] at 7 T enabled assessment of cellular metabolite changes with excellent spatial resolution in the rat heart. A higher field strength such as 7 T is important to establish a gold standard for quantification of myocardial metabolism by providing accuracy and precision in biochemical quantification.

Recently, a first-in-human study [76] using the DNP hyperpolarization technique was successfully conducted on patients with prostate cancer and suggested the safety and feasibility of hyperpolarized $[1-^{13}\text{C}]$ pyruvate injections. Cunningham et al. [21] were the first to use hyperpolarized ^{13}C MRS in the human heart, revealing the $[^{13}\text{C}]$ bicarbonate signal in the LV myocardium and the lactate signal in both the cardiac chambers and the myocardium (Fig. 9). Pyruvic acid has been the most widely used substrate in hyperpolarized ^{13}C studies and was used in the first clinical study. Recently, $[1-^{13}\text{C}]$ lactic acid and $[1-^{13}\text{C}]$ butyric acid as samples in DNP have been used to assess cardiac pyruvate dehydrogenase flux and short-chain fatty acid metabolism in animals [77,78]. Further studies in humans with various substrates are needed to obtain additional important information on metabolite-based diagnostic and therapeutic

outcomes. In addition, hyperpolarized ^{13}C metabolic imaging has the potential to improve diagnosis and prognosis and to monitor therapeutic response at the cellular level through assessment of heart disease-oriented biochemical pathways, together with cardiac perfusion imaging with hyperpolarized ^{13}C urea and pH mapping with the Henderson-Hasselbalch equation ($\text{pH} = \text{pK}_a + \log_{10} \text{HCO}_3^- / \text{CO}_2$, with $\text{pK}_a = 6.15$) (Fig. 10) [36,79]. Hyperpolarized ^{13}C MRS will be useful for early detection of heart diseases and metabolic mapping of perfusion and intracellular pH.

CONCLUSION

Cardiac MRS provides fundamental information on changes in myocardial metabolism, especially in ischemic heart disease and heart failure. Although ^1H and ^{31}P MRS have limited clinical roles, cardiac MRS is becoming increasingly important in both early detection of and evaluation of the therapeutic response in heart diseases. Together with the use of higher field strength, more accurate outcomes are expected due to enhanced temporal and spatial resolutions. Furthermore, advanced hyperpolarized ^{13}C MRS might lead to development of important diagnostic biomarkers for assessment of various heart diseases by providing additional metabolic information.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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