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REVIEW

Magnetic resonance imaging of cardiac metabolism in heart failure: how far have we come?

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As one of the highest energy consumer organs in the body, the heart requires tremendous amount of adenosine triphosphate (ATP) to maintain its continuous mechanical work. Fatty acids, glucose, and ketone bodies are the primary fuel source of the heart to generate ATP with perturbations in ATP generation possibly leading to contractile dysfunction. Cardiac metabolic imaging with magnetic resonance imaging (MRI) plays a crucial role in understanding the dynamic metabolic changes occurring in the failing heart, where the cardiac metabolism is deranged. Also, targeting and quantifying metabolic changes *in vivo* noninvasively is a promising approach to facilitate diagnosis, determine prognosis, and evaluate therapeutic response. Here, we summarize novel MRI techniques used for detailed investigation of cardiac metabolism in heart failure including magnetic resonance spectroscopy (MRS), hyperpolarized MRS, and chemical exchange saturation transfer based on evidence from preclinical and clinical studies and to discuss the potential clinical application in heart failure.

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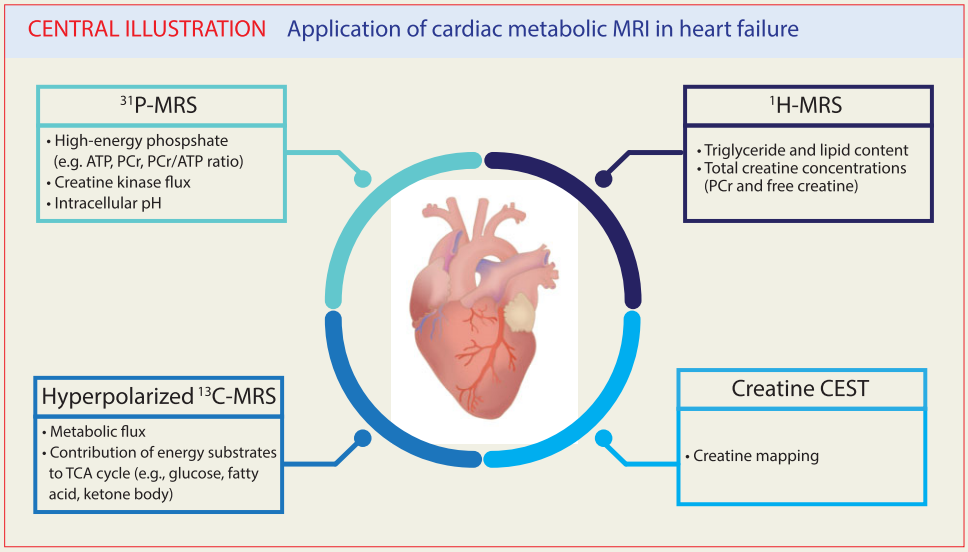
Graphical Abstract



Key parameters of cardiac metabolic MRI for the assessment of myocardial metabolism in heart failure. ATP, adenosine triphosphate; MRI, magnetic resonance imaging; PCr, phosphocreatine; TCA, tricarboxylic acid.

Keywords cardiac metabolism • heart failure • magnetic resonance imaging • magnetic resonance spectroscopy • hyperpolarized MRS

Highlights

- The chronically failing heart has been shown to be metabolically abnormal.
- Cardiac metabolic magnetic resonance imaging (MRI) provides comprehensive information about various aspects of myocardial metabolism *in vivo* [e.g. high-energy phosphate, creatine kinase (CK) system, lipid content, metabolic flux], suited for a real-time and serial follow-up study due to its non-invasive nature.
- Cardiac metabolic MRI has the potential to emerge as a non-invasive tool to facilitate diagnosis, monitor disease progression, determine prognosis, and evaluate the effects of therapy in heart failure (HF).

Metabolic flexibility is essential for a healthy heart to function properly under constantly changing milieu conditions.[1] Although making up only a small fraction of our total body mass, the heart consumes more energy per gram of tissue than any other human organ. Of this, the heart consumes around 6 kg of adenosine triphosphate (ATP) per day, about 15–20 times of its own weight.[2,3] Within the heart, increased energy demands drive compensatory metabolic changes to maintain energy homeostasis by switching metabolic substrates. Adult heart primarily utilize fatty acid (FA), a small amount of glucose, and to some extent also ketone bodies.[4] The contribution of these substrates to ATP production depends on the substrate availability, hormonal status, dietary pattern, energy demand ,and 'metabolic flexibility' of the heart.[1,5]

The myocardial CK system plays a vital role in rapid energy supply during increased workload, because it can supply ATP faster than that from other pathways.[6] Creatine has long been regarded as a vital metabolite in the network of energy transfer,[7] as it can be phosphorylated into phosphocreatine (PCr) which acts as an energy buffer to maintain ATP constant concentrations constant.[3] With the development of HF, the metabolic flexibility of the heart is diminished.[2,8] This results in up to ~30% reduction in ATP production and consequently affects cardiac contractility.[7] The decline in high-energy phosphate metabolism has important implications in HF and is correlated with LV dysfunction severity.[7,9]

Recent data from animals and human studies suggest that the failing heart shifts from using FAs as the preferred substrate to become more reliant on glucose oxidation with associated increases in ketone metabolism; however, the relative contribution of these substrates to total ATP production is relatively low.[2,10] Over the past decade, there has been a growing interest in targeting cardiac metabolism as a therapeutic approach for HF.[11] Research exploring the unique metabolic remodelling of the failing heart has led to the proposal of a new metabolic treatment for HF, including ketone bodies, that may enhance cardiac energetics and exert pleiotropic effects in a way that could be beneficial for the failing heart.[5,12,13]

Noninvasive assessment of myocardial energy production *in vivo* in healthy state and perturbed cardiac metabolism observed in HF is important as it may provide a better understanding of HF

Table 1 Cardiometabolic MRI studies in humans with HF

First author and year	Imaging method	N, participants	Major outcomes
Neubauer *et al.*[14]	Cardiac ^{31}P-MRS	33 patients (14 with CAD and 19 with DCM) and 19 healthy controls	Cardiac high-energy phosphate metabolism at rest was normal in LAD stenosis and chronic MI in the absence of HF; and that it was correlated with HF severity in DCM.
Weiss *et al.*[15]	Cardiac^{31}P-MRS	16 patients with CAD and ischaemia, 9 with nonischaemic heart disease, and 11 healthy controls	During hand-grip exercise, myocardial PCr/ATP ratio was reduced in patients with CAD and ischaemia, while patients with non-ischaemic cardiomyopathy and those with ischaemic heart disease after revascularization therapy had preserved myocardial PCr/ATP.
Neubauer *et al.*[16]	Cardiac^{31}P-MRS	39 patients with DCM	Myocardial PCr/ATP ratio was correlated with LVEF, and it was a significant predictor both total and cardiovascular mortality in DCM.
Okada *et al.*[17]	Cardiac^{31}P-MRS	10 patients with HCM and 15 healthy controls	Both PCr and ATP content were lower in patients with HCM.
Beer *et al.*[18]	Cardiac^{31}P-MRS	10 patients with DCM and 10 healthy controls	PCr was reduced by 51%, ATP by 35%, and PCr/ATP by 25% In patients with DCM. Myocardial energetic was correlated with functional parameters (LV volume, EF), with the strongest correlations for PCr.
Weiss *et al.*[19]	Cardiac ^{31}P-MRS	17 patients with HF and 16 normal subjects	Cardiac PCr was reduced 18% in in CHF patients. ATP concentrations were unchanged. CK flux was reduced 50% compared with normal subjects.
Hansch *et al.*[20]	Cardiac ^{31}P-MRS	20 healthy controls and 15 patients with severe symptoms (LVEF < 30%) and 10 patients with moderate symptoms (LVEF > 30%) of DCM	Reduced PCr/ATP ratio was observed in patients suffering from DCM.
Lee *et al.*[21]	^{31}P-MRS	56 patients with CHF	Treatment with perhexiline led to significant improvements in skeletal muscle PCr recovery by 34%.
Chida *et al.*[22]	Cardiac ^{31}P-MRS	20 cardiac patients (13 DCM, 3 HCM, 3 HHD, and 1 aortic regurgitation)	The myocardial PCr/ATP ratio was significantly lower in DCM patients (1.82 ± 0.33), and in patients with global myocardial dysfunction (1.89 ± 0.32) than in healthy volunteers (2.96 ± 0.59).
Smith *et al.*[23]	Cardiac ^{31}P-MRS	20 LVH patients with and without CHF, and 14 healthy controls	Mean myocardial cardiac PCr was reduced by 30% in both LVH and LVH with CHF, without any changes in ATP. No difference between LVH group with and without CHF. Net CK flux was reduced by 30% in the LVH group. Mean CK flux was reduced by 65% and 30% in the LVH with CHF group when compared with normal subjects and those with LVH, respectively.
Shivu *et al.*[24]	Cardiac ^{31}P-MRS	26 patients with HCM and 37 healthy controls	The PCr/ATP ratio was significantly reduced in HCM patients compared to controls (1.42 ± 0.51 and 2.11 ± 0.57, respectively).
Hirsch *et al.*[25]	Cardiac ^{31}P-MRS	16 patients with nonischaemic cardiomyopathy	Treatment with allopurinol increased PCr/ATP ratio, PCr concentration, CK flux, free energy of ATP hydrolysis in the failing heart.
Bottomley *et al.*[26]	Cardiac ^{31}P-MRS	58 HF patients with nonischaemic cardiomyopathy	During follow up for a median 4.7 years, risk of HF-related composite outcomes decreased by 32–39% for every 1 $\mu mol\ g^{-1}\ s^{-1}$ increase in CK flux.
Beadle *et al.*[27]	Cardiac ^{31}P-MRS	50 patients with nonischaemic HF	Perhexiline therapy was associated with a 30% increase in the PCr/ATP ratio (vs. a 3% decrease with placebo).
Dass *et al.*[28]	Cardiac ^{31}P-MRS	35 HCM patients and 20 healthy controls at rest and during leg exercise	Resting PCr/ATP ratio was significantly reduced in HCM than control (1.71 ± 0.35, vs. 2.14 ± 0.35 respectively). There was a further reduction in PCr/ATP in HCM group during exercise (1.56 ± 0.29, compared with rest) but not in healthy controls.
Schär *et al.*[29]	Cardiac ^{31}P-MRS	17 patients with HF and 12 healthy subjects	Using two-repetition time ST (TwiST) method, significant reductions in the pseudo-first-order rate constant (CK k_f) was detected in HF patients compared to healthy subjects.

Continued

Table 1 Continued

First author and year	Imaging method	N, participants	Major outcomes
Stoll *et al.*[30]	Cardiac ^{31}P-MRS	25 patients with DCM and 10 healthy controls	Patients with DCM had a significantly lower PCr/ATP than healthy subjects (1.54 ± 0.39 vs 1.95 ± 0.25).
Gabr *et al.*[31]	Cardiac ^{31}P-MRS	27 patients with HF and 24 healthy subjects	The concentrations of PCr and ATP and the CK rate-constant kf were reduced in HF patients by 13–19%. CK flux was reduced by 32%. CK flux was correlated with energy utilization and reduced cardiac mechanical work.
Solaiyappan *et al.*[32]	Cardiac ^{31}P-MRS	45 healthy subjects and 109 patients with non-ischaemic cardiomyopathy. Of the 109 patients some had LVH with no evidence of critical coronary disease, 38 patients were diagnosed with HCM.	Neural networks employing ^{31}P-MRS measures (ATP, PCr, the first order CK reaction rate kf, CK flux) had an accuracy of 84% in discriminating healthy, HF and non-HF cardiac disease. The neural network also distinguished HF patients with DCM, hypertrophy, and NYHA class with around 80% accuracy.
Burrage *et al.*[33]	Cardiac ^{31}P-MRS	Patients across the spectrum of diastolic dysfunction and HFpEF (9 with T2D,14 with HFpEF; and 9 with cardiac amyloidosis) and 11 healthy controls	Reduced PCr/ATP ratio existed across the spectrum of HFpEF, and it was correlated with disease severity including NYHA class, NT-proBNP, and echocardiographic E/e′ ratio.
Rayner *et al.*[34]	Cardiac ^{31}P-MRS	16 patients with normal weight and DCM (DCM_{NW}), 27 with obesity and DCM (DCM_{OB}), and 26 normal weight controls (CTL_{NW}) 19 DCM_{OB} patients underwent repeat assessment after a dietary weight loss intervention	Myocardial PCr/ATP was reduced in DCM. Weight loss intervention prevented fall in PCr/ATP ratio and increased median CK flux during dobutamine stress test.
Nakae *et al.*[35]	Cardiac ^{1}H-MRS	Patients with either DCM (11) or HCM (7) and healthy controls (14)	Myocardial creatine was lower in both patients with DCM (16.1 ± 4.5) and HCM (22.6 ± 8.1 μmol/g) compared to healthy hearts (27.6 ± 4.1 μmol/g). Myocardial creatine correlated positively with LVEF and negatively with plasma BNP.
Nakae *et al.*[36]	Cardiac ^{1}H-MRS	15 patients with CHF and 14 healthy controls	Myocardial creatine was significantly lower in failing hearts than in healthy hearts (15.1 ± 5.0 vs. 27.6 ± 4.1 μmol/g), correlated negatively with plasma BNP.
Nakae *et al.*[37]	Cardiac ^{1}H-MRS	14 patients (2 with cardiac amyloidosis, 4 with HHD, 2 with valvular heart disease, 2 with HCM, 2 with DCM, 1 with restrictive cardiomyopathy and 1 with post-operative atrial septal defect) and 10 healthy controls	Myocardial creatine levels in diseased hearts were significantly lower than healthy hearts (16.5 ± 6.0 vs 27.1 ± 3.2 μmol/g) and was positively correlated with LVEF. Myocardial creatine content in patients who were hospitalized due to HF within 1 year was significantly lower than those in other patients.
Nakae *et al.*[38]	Cardiac ^{1}H-MRS	8 patients with HCM, 12 with DCM, 10 with ischaemic cardiomyopathy, and 22 healthy subjects	Myocardial triglyceride was lower in HCM and higher in ischaemic cardiomyopathy, while there was no difference between DCM and healthy hearts. Myocardial creatine was lower in HCM, DCM and ischaemic cardiomyopathy, and it was correlated with LVEF and FA uptake.
Liao *et al.*[39]	Cardiac ^{1}H-MRS	50 AHF patients and 21 healthy controls	Patients who were discharged after hospitalization for AHF (with low EF and normal EF) had increased myocardial UFA content than controls (0.79% vs. 0.21% vs. 0.14%, respectively).
Zamani *et al.*[40]	Leg creatine CEST	19 patients with hypertension, 20 with HFpEF, and 20 healthy controls	Impaired skeletal muscle oxidative phosphorylation capacity was found in patients with HFpEF, evidenced by longer half-time of creatine recovery.

CAD, coronary artery disease; HHD, hypertensive heart disease.

development as well as targets for future therapies. Despite this recognition, cardiac metabolism is not routinely assessed in clinical practice. At present, magnetic resonance (MR) metabolic imaging uses techniques including MR spectroscopy (MRS), hyperpolarized MRS, and chemical exchange saturation transfer (CEST) imaging to visualize and quantify metabolites (*Graphical abstract*). Unlike metabolic imaging using positron emission tomography (PET) that requires radioactive tracers and PET does not distinguish injected tracer from its metabolic products, MRI metabolic imaging allows for in vivo assessment of many aspects of cardiac metabolism in the normal and diseased heart that may lead to better characterization, prevention, and treatment of HF. In *Table 1*, we summarize clinical studies using cardiac metabolic MRI to image myocardial metabolism in a dedicated HF setting. For more detailed descriptions of the techniques on how to obtain the images and quantify the results, we refer the reader to the various technical reviews on this topic.[41–43]

Cardiac metabolic imaging: imaging modalities

MRS

Nuclear MRS, more commonly known as MR spectroscopy or MRS, is a non-invasive contrast-free technique, which can be used to study the presence and concentration of various metabolites in vivo in the myocardium without the use of ionizing radiation.[44] NMR was first described by Felix Bloch and Edward Mills Purcell in 1946. But it was not until more than two decades later that this technique was applied in cardiology field when the first ^{31}P-MRS was demonstrated in isolated heart by Oxford group (Pamela Garlick, George Radda and John Seeley) in the 1970s.[45] MRS is a spectroscopic technique that observes the effect of intramolecular magnetic fields on the nuclei of interest when placed in a magnetic field and probed with radio frequency pulses. These intramolecular magnetic fields induce different shifts in resonant frequencies (or 'chemical shifts') dependent on the molecular electronic structure and functional groups and are often uniquely characteristic of individual molecules of interest.[44] Generally, these molecules of interest from the heart are referred to as 'metabolites' and typically each metabolite will exhibit a unique chemical shift that can change as the metabolite metabolizes to another downstream metabolite. Furthermore, cardiac MRS can be acquired from a range of different nuclei, including ^{31}Phosphorus (^{31}P) and ^{1}Proton (^{1}H), in which each of these nuclei can be used to assess different aspects of cardiac metabolism.

MRS has been mostly applied clinically for brain tissue, some of which have been implemented in clinical practice (i.e. to identify primary brain tumours, tumour aggressiveness, and evaluate after treatment).[46] Currently, cardiac MRS is not widely performed in routine clinical examinations due to various technical challenges including but not limited to limited clinically available field strengths, susceptibility to field inhomogeneity, non-standardization of post processing of spectra, and lack of infrastructure for non-proton metabolites. Most clinical cardiac studies typically are performed at 1.5 T or 3.0 T and thus a majority of cardiac MRS studies are performed at these field strengths.[14,19,24,33] Generally, increasing the field strength improves signal-to-noise ratio (SNR) and the metabolite peaks separation, and thus, MRS could potentially improve at higher field strengths (e.g. 7 T) with a few studies demonstrating improved sensitivity to high energy phosphates.[47,48] Higher field strengths unfortunately incur increased field inhomogeneity, which can introduce artefacts and remain an active area of research. Post processing to effectively separate, identify, and quantify the metabolite peaks are not completely standardized and require local technical expertise to ensure quality assurance of data.[49,50] This fragmentation is a consequence of the vibrant MRS research community but has led to challenges in standardizing measurements and reported values. Finally, it should be noticed that, if MRS is used to observe non-proton nuclei, then additional hardware including nucleus-specific coils and radiofrequency (RF) power amplification are also required adding to the complexity and cost of performing such studies.[44,51] These hardware requirements are significant infrastructural challenges and again are not standardized in routine clinical environments.

In general, conventional ^{1}H-MRI is first acquired to confirm and guide the appropriate anatomical voxel selection and surface coil placement for spectroscopic interrogation. The nuclei-specific coils and RF for cardiac MRS examinations should be placed appropriately to minimize the distance between the heart and the coil and the effects of respiratory motion. MR spectra can be spatially localized with several sequences such as depth-resolved surface coil spectroscopy, image-selected in vivo spectroscopy, or chemical shift imaging.[44,52] Furthermore, synchronization with cardiac-induced motion using cardiac gating technique is required.[53,54] There are several ways to quantify metabolite concentrations from MRS, including absolute quantification using internal (i.e. ^{1}H-MRS-measured tissue water as a reference standard) and external references (e.g. phantoms), and relative methods using metabolite ratios (e.g. PCr/ATP ratio).[55]

^{31}P spectroscopy

Within the heart, the most abundant phosphorous-containing metabolites are ATP, adenosine diphosphate (ADP), adenosine monophosphate, PCr, inorganic phosphate (Pi), 2,3-diphosphoglycerate, and phosphodiesters. ^{31}P-MRS is frequently used to determine the PCr/ATP ratio, which is used as a marker for cardiac energy metabolism in the literature (*Figure 1*). Intracellular pH can also be quantified by means of comparing of the chemical shift between the Pi and PCr resonances.[56] Furthermore, ^{31}P-MRS and magnetization transfer techniques can be utilized to measure *in vivo* metabolic fluxes via CK and ATP synthase.[57] Other than the readouts mentioned above, the Gibbs free energy can also be estimated by measuring total creatine combined with ^{31}P-MRS readouts.[58]

Preclinical and clinical studies have firmly recognized perturbed energy metabolism as a hallmark of the failing heart. Imaging of cardiac energetics using ^{31}P-MRS has been investigated in preclinical animal models and humans with HF. Studies in a mouse model of pressure-overload showed that hypertrophic hearts had 25% lower PCr/ATP ratio compared to controls.[59,60] In another study, myocardial creatine phosphate in a rat model of triiodothyronine and isoproterenol-induced cardiac hypertrophy was reduced by 45% and 25% respectively.[61] Reduction of PCr/ATP ratio was also observed in a swine model of pacing-induced dilated cardiomyopathy (DCM).[62]

One of the earliest studies by Neubauer *et al.*[14] showed that cardiac energy phosphate metabolism was normal in patients with left anterior ascending artery (LAD) stenosis and chronic myocardial infarction (MI) without HF, and that it was correlated with HF severity

in DCM. Moreover, reduction of PCr/ATP ratio in DCM was correlated with the New York Heart Association (NYHA) class[14] and with left ventricular ejection fraction (LVEF), suggesting that PCr/ATP ratio decrease in advanced HF but initially remains normal.[16] In agreement, previous studies demonstrated that reduction of PCr/ATP ratio was also observed in patients with DCM[20,22,30] and hypertrophic cardiomyopathy (HCM).[24,28] In a recent study, Burrage *et al.*[33] reported decreased PCr/ATP ratio in patients across the spectrum of diastolic dysfunction and HF with preserved ejection fraction (HFpEF), and the energy deficit severity was correlated with NYHA class, NT-proBNP and echocardiographic E/e′ ratio.

Some studies also used ^{31}P-MRS to monitor the effects of pharmacological and non-pharmacological intervention on cardiac energetics. For example, treatment with ACE inhibitors, digitalis, diuretics and beta-blockers for 3 months improved PCr/ATP ratio in DCM patients.[14] Hirsch et al reported that a xanthine oxidase inhibitor allopurinol increased PCr/ATP ratio, PCr concentration, and CK flux in HF patients.[25] In patients with non-ischaemic chronic HF, perhexiline normalized skeletal muscle PCr recovery after exercise[21] and increased myocardial PCr/ATP ratio by 30%[27]. Interestingly, dietary weight loss intervention was also reported to improve myocardial energetics in patients with DCM and obesity.[34]

Additionally, PCr/ATP ratio may also provide additional prognostic information on survival of patients with HF. In patients with DCM, myocardial PCr/ATP more accurately helped predict long-term survival than NYHA class or LVEF.[16] In a prospective study following 58 patients with nonischaemic cardiomyopathy for a median of 4.7 years, Bottomley *et al.*[26] demonstrated that even after correction for NYHA class, LVEF, and race, CK flux was a significant predictor of HF outcomes. Furthermore, risk of HF-related composite outcomes decreased by 32–39% for every 1 μmol g^{-1} s^{-1} increase in CK flux.

Of note, data from experimental study demonstrated that both PCr and ATP levels decrease in parallel in HF[63]; therefore, the changes in cardiac energetics in HF is often underestimated when PCr/ATP ratio is used rather than measurement of absolute PCr and ATP concentrations, especially during the early stage of HF development. However, measurement of the absolute concentrations of PCr and ATP *in vivo* using ^{31}P-MRS is more challenging as it requires (external) concentration reference (e.g. myocardial tissue from biopsy, phantom) and acquisition adjustments (e.g. sensitivity profile of the radio-frequency coil). Reduced PCr levels without change in ATP were observed in patients with cardiac hypertrophy and normal cardiac function ,[23] while in patients with DCM, both PCr and ATP were reduced but the reduction of PCr was more severe.[17,18] In DCM, Beer et al also showed that PCr levels were decreased by 51% while ATP levels by 35%, and the PCr/ATP ratio was reduced by 25% only.[18] A significant correlation was also found between LV volume/EF and cardiac energetics, with the strongest correlation observed for PCr and the weakest correlation observed for PCr/ATP ratio.[18] Recent study using combination of cardiac pressure-volume loops, MRI, and ^{31}P-MRS showed connection between reduced cardiac mechanical work with reduced CK flux in patients with HF.[31] Additionally, neural network analysis employing ^{31}P-MRS readouts were able to distinguish HF and NYHA class with clinically relevant accuracy.[32]

Other than indices described above, ^{31}P-MRS can also be used to determine the changes in the kinetic of CK shuttle, sensitive marker of myocardial energetics. Significant reductions in myocardial CK pseudo first-order rate (CK k_f) were observed in patients with HF compared to healthy subjects.[23,29,64] Recently, a new method combining a shorter 'stressed saturation transfer' extension to the triple repetition time saturation transfer method has been introduced at 3T that enabled the quantification of myocardial CK k_f in the supine position.[65]

Advantages and limitations

Unlike conventional biochemical analysis which requires tissue biopsy, ^{31}P-MRS can provide cardiac energetics readouts and metabolic fluxes noninvasively. Notably, longitudinal study with repeated measurements of high-energy phosphates can be measured on the same animal or subjects; something that cannot be done by biochemical means. However, ^{31}P-MRS does not provide information about the rate of ATP production and/or of ATP utilization. Also, ^{31}P-MRS has inherently lower sensitivity compared to proton and limited spatial resolution. To overcome these limitations, recent technical advancements such as spatial localization with optimal point-spread function[66] can be employed and acquiring at ultra-high-field strength (≥7 T) will increase the MRS sensitivity, improve SNR and shorter measurement time.[47]

^{1}H spectroscopy

Protons (^{1}H) have the highest sensitivity and natural abundance of all nuclei, and hence, endogenous protons produce large MR signal. ^{1}H is found in many metabolites including creatine, lactate, carnitine, taurine, and lipids. *In vivo* cardiac ^{1}H-MRS has been studied to quantify myocardial triglyceride content in both healthy[67,68] and diseased hearts[35,36] Using ^{1}H-MRS, the chemical composition of the fat can be determined by measuring the relative amplitudes of the peaks in the fat spectrum that correspond to different positions within the triglyceride molecule (based on amount of the methyl and methylene resonances), although contribution from other lipids such as cellular phospholipids as well as other FA-containing lipid cannot be excluded.[69,70] Besides quantification of myocardial fat content, ^{1}H-MRS has the potential to measure total creatine concentrations (i.e. both PCr and free creatine) (*Figure 2*). Free creatine concentration can also be calculated by measuring total creatine concentration *in vivo* using ^{1}H-MRS and subtracting the PCr concentration determined with ^{31}P-MRS[71]; thus, the Gibbs free energy (ΔG) can then be estimated using the ADP, ATP, and Pi concentrations.[19] Single-voxel or spectroscopic imaging sequences, such as stimulated echo acquisition mode,[72] point resolved spectroscopy,[19] spin-echo full-intensity acquired localized spectroscopy,[73] or (semi-) localization by adiabatic selective refocusing (semi-LASER and LASER),[74,75] can be used for ^{1}H-MRS.

Until now, there are only few studies assessing myocardial lipid metabolism and creatine using ^{1}H-MRS in cardiomyopathy and HF. Myocardial triglyceride content has been reported to predict diastolic dysfunction in diabetes[76] and aging male heart.[77] Myocardial triglyceride was significantly lower in HCM and higher in ischaemic cardiomyopathy, while there was no difference between DCM and healthy hearts.[38] Interestingly, Nakae *et al.*[38] also suggested that myocardial triglycerides content did not correlate with cardiac dysfunction. Reduced myocardial unsaturated FA was also reported in

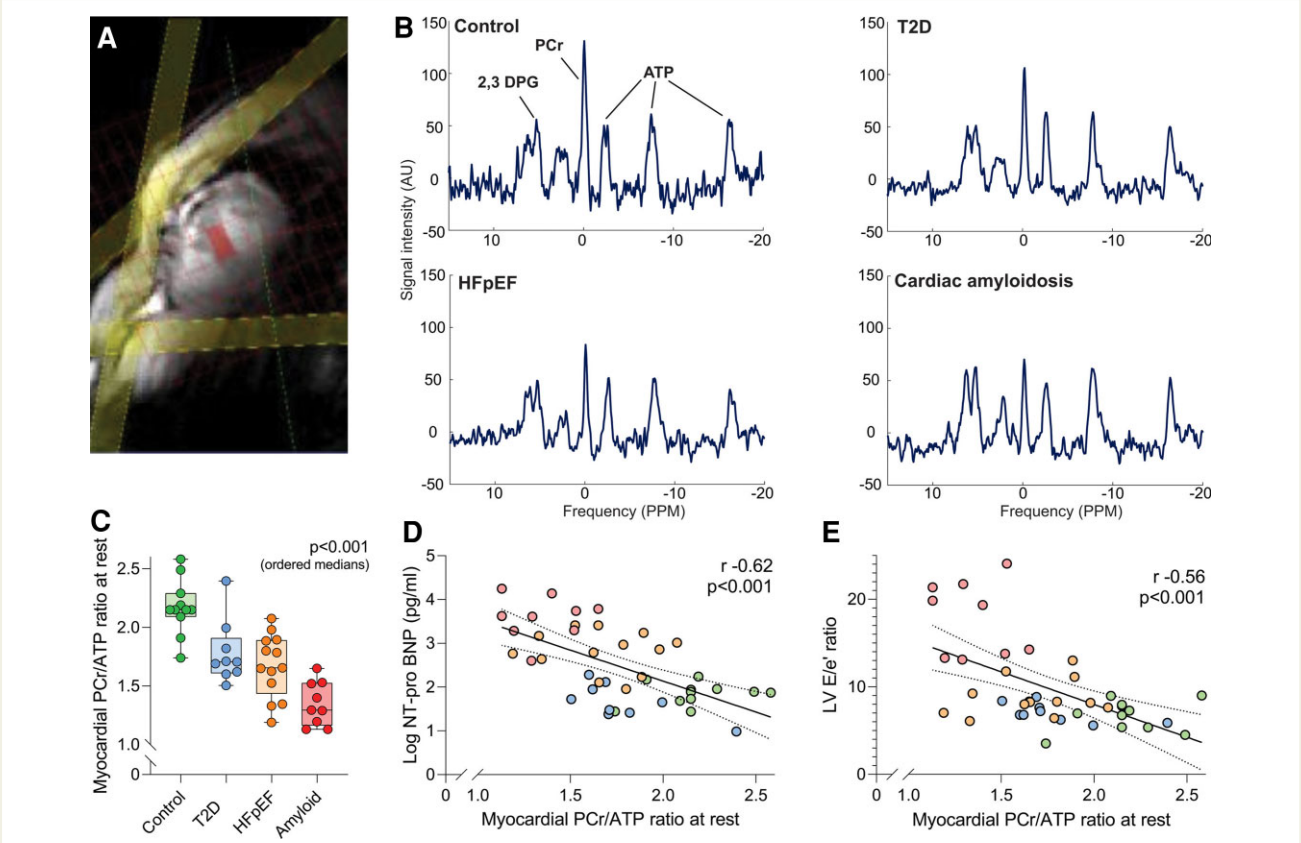


Figure 1 (*A*) Representative ^{31}P-MRS acquisition strategy with a voxel placed in the midventricular septum (red) and saturation bands (yellow) placed over skeletal muscle and the liver. (*B*) Representative cardiac ^{31}P-MR spectra of healthy control, patients with type 2 diabetes (T2D), HFpEF, and cardiac amyloidosis. (*C*) Myocardial PCr/ATP ratio of all groups. Associations of PCr/ATP ratio with (*D*) NT-proBNP and (*E*) LV E/e′ ratio. Adapted from [33] with permission.

patients who were discharged after hospitalization for acute HF (AHF).[39]

In a series of elegant studies, Nakae *et al.*[35–38] showed that patients with non-ischaemic HF (secondary to DCM, HCM, restrictive cardiomyopathy, valvular heart disease, hypertensive heart disease or cardiac amyloidosis) had reduced myocardial total creatine content. Myocardial creatine content was correlated positively with LVEF[35,37,38] and FA uptake[38] and negatively with plasma BNP.[35,36] Using ^{1}H-MRS and^{31}P-MRS, Hirsch *et al.*[25] demonstrated that allopurinol reduced concentration of ADP and increased ΔG_{ATP} in patients with HF. Furthermore, myocardial creatine content in patients who were hospitalized due to HF within 1 year were significantly lower than those in other patients, suggesting that it may be correlated with the degree of myocardial cellular damage in the diseased heart.[37]

Advantages and limitations

^{1}H-MRS can determine myocardial lipid and creatinine contents without invasive biopsy, allowing for repeated measurements in longitudinal studies. Cardiac ^{1}H-MRS requires the same hardware (i.e. magnet, gradient, and RF coils) as any cardiac MRI protocol. Major challenges for ^{1}H-MRS include the necessity for excellent suppression of the strong ^{1}H signal from water, excellent shimming, and motion compensation. ^{1}H-MRS often requires larger voxel sizes and longer scan times that limit its clinical use. To overcome this, fast spectroscopic imaging of both cardiac triglyceride and total creatine content using optimized echo-planar spectroscopic imaging sequence has been introduced but continue to be an active area of research.[78] Also, other limitations that need to be considered are the physiological factors such as nutritional status (feeding or fasting state) and exercise that may influence the lipid content abundance, making it very difficult to compare across these variables.[79–81]

Hyperpolarized^{13}carbon (^{13}C) spectroscopy

Tracing of carbon atoms through multiple metabolic pathways is an invaluable tool for investigating dynamic metabolic changes occurring in health and disease. Conventional method to trace carbon *in vivo* utilizes MRS of stable isotope ^{13}C, following injection of ~100% ^{13}C-enriched metabolites such as ^{13}C-glucose to overcome the low natural abundance of ^{13}C (1.1%). The ^{13}C labels are transferred to downstream metabolites through enzymatic reactions in *vivo*, resulting in multiple peaks in the ^{13}C spectrum, allowing quantitative analysis of metabolic flux in organ.[82,83] However, due to the low NMR sensitivity of ^{13}C (~ 1.6% that of ^{1}H), the conventional ^{13}C-MRS requires long scan time and suffers from poor spatial and temporal resolutions. To overcome these limitations,

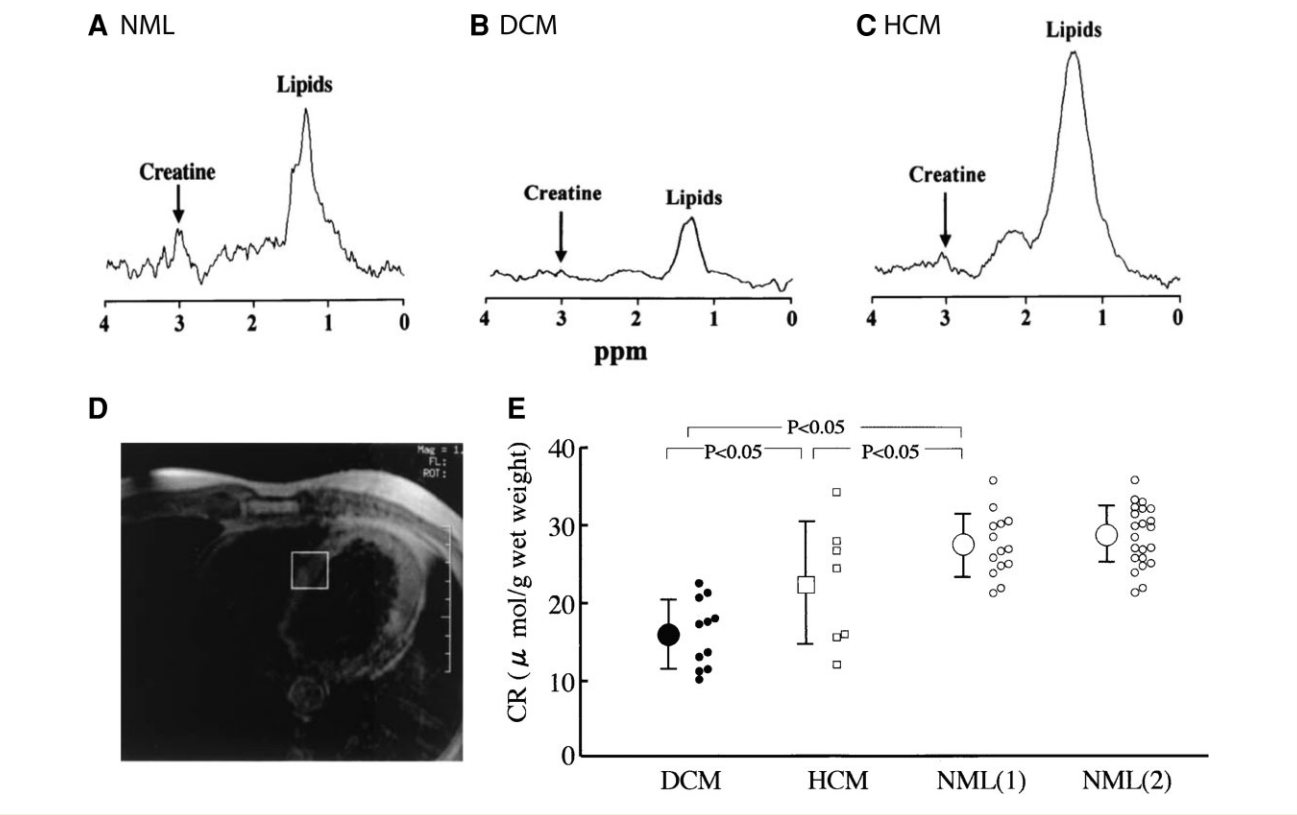


Figure 2 Representative cardiac ^{1}H-MR spectra of (*A*) a healthy control, patient with (*B*) DCM and (*C*) HCM. (*D*) Representative spin-echo MRI. (*E*) Myocardial creatine content of all groups. NML, normal/healthy controls; NML(1), age-matched normal control group; NML(2), non–age-matched larger normal control group; CR, creatine. Modified from [35], with permission.

hyperpolarization was introduced to dramatically increase the spin alignment (or polarization) of exogenous ^{13}C-enriched substrates, yielding a signal enhancement of more than 10 000-fold,[84] *in vivo* after injection of the substrate, allowing for rapid assessment of ^{13}C metabolism *in vivo*.[42,83]

Hyperpolarization MRS is an emerging technology that requires specialized hardware to improve polarization by either dynamic nuclear polarization (DNP)[84] or parahydrogen-induced polarization (PHIP).[85] DNP is the most common form of hyperpolarized MRS, currently employed in more than 30 clinical trials, and yields high polarization levels by rapidly cooling down a molecule of interest to near 1 Kelvin in a high magnetic field (3 T to 10 T) and irradiating electron spins by microwave to dynamically transfer electron polarization to nuclear spin.[84] PHIP generates spin polarization by transferring parahydrogen to the target molecule through a chemical reaction of breaking a double bond. For most cardiac metabolic imaging applications, hyperpolarized ^{13}C-MRS is achieved via DNP given its flexibility in the molecule of interest which is not restricted to the double bond requirement of PHIP.[85]

Hyperpolarized ^{13}C-MRS via DNP requires rapid dissolution of the frozen, hyperpolarized ^{13}C substrate by heated solvent within 1–2 s to retain the high-degree polarization and neutralize pH in the injectable solution. The lifetime of the dissolved hyperpolarized ^{13}C substrate is limited by the ^{13}C T_1 relaxation rate, which ranges from 1–3 min^{-1}. To benefit from a hyperpolarized liquid state solution, rapid transfer (through injection) into the subject is required, followed by efficient and rapid ^{13}C spectroscopic imaging sequences.[44,83] Myocardial substrate utilization, citric acid cycle flux, pyruvate dehydrogenase flux, beta-oxidation of FA can then be quantified.[83]

For cardiac ^{13}C-MRS study, the heart must be supplied with labeled compounds such as pyruvate ([1-^{13}C]pyruvate to quantify pyruvate dehydrogenase flux or [2-^{13}C]pyruvate to allow investigation of Krebs cycle metabolism),[86] butyrate (FA metabolism),[87] or acetoacetate and beta-hydroxybutyrate (ketone body metabolism).[88] These enable investigation of cardiac FA, glucose, and ketone body metabolism, which may well be perturbed in HF.

Cardiac hyperpolarized ^{13}C-MRS has been studied in various preclinical model of HF. Experimental study in rats with cardiac hypertrophy (through abdominal aortic banding) resulted in unchanged PDH flux but increased lactate production, suggesting of enhanced glycolysis.[89] In a rat model of diabetic cardiomyopathy, PDH flux was reduced and treatment with PDK inhibitor dichloroacetate could normalize this level, [90] while in rats with doxorubicin-induced cardiomyopathy, both PDH flux and Krebs cycle flux were decreased.[91] Intriguingly, study in mice carrying *Lmna*$^{H222P/H222P}$ mutation (a model for DCM) demonstrated that metabolic dysfunction, marked by reduced pyruvate/lactate exchange rate, was detected well before the disease can be detected by echocardiography.[92] Labelling both pyruvate and acetoacetate, a study in obese rats

with spontaneously hypertensive HF treated with empagliflozin showed reduction of myocardial ketone utilization without changing glucose utilization *in vivo*.[93]

A study in a swine model of pacing-induced DCM showed pyruvate oxidation was maintained until DCM developed.[62] Increased lactate/bicarbonate ratio was detected in a porcine model of right ventricular HF, indicating a shift towards anaerobic metabolism.[94] Reduced PDH flux was identified in swine with right ventricular HF, and treatment with dichloroacetate augmented carbohydrate metabolism and improved cardiac phenotype in this model.[95] In a porcine model of HFpEF with a predominant background of hypertension, PDH flux was increased indicating a switch towards glucose substrate utilization.[96] In 2016, Cunningham *et al.*[97] reported the first experimental study using cardiac hyperpolarized [1-^{13}C]pyruvate in humans. Although there have been no published studies applying hyperpolarized ^{13}C-MRS in humans with HF, this technique holds potential to assess cardiac metabolic flux *in vivo*.

Advantages and limitations

Hyperpolarized ^{13}C-MRS allows direct real-time measurement of metabolic flux in multiple metabolic pathways and individual contribution of energy substrates to tricarboxylic acid cycle *in vivo*. This technique is suitable for longitudinal studies to detect metabolic changes in disease progression and treatment effects. Of note, application in humans requires a hyperpolarizer in close proximity of the MR scanner and an FDA-IND approved workflow for substrate preparations and real-time quality control of the hyperpolarized probe molecules in the clinic. Specialty hardware, including multi-nuclear MR system and ^{13}C coils, as well as ^{13}C MR sequences for rapid spectroscopic imaging within the lifetime of the hyperpolarized ^{13}C probes are required. Reliability and cross-platform reproducibility are current subjects of investigations before this novel technique can be disseminated for multi-centre clinical trials.

CEST

CEST is an emerging MRI technique for metabolic imaging which exploits the chemical exchange between solute and water protons. In principle, the exchanging proton, possessing a chemical shift distinct from water, is selectively saturated and the saturation is transferred to the bulk water via chemical exchange.[98,99] MRI based on CEST can be applied to map different metabolites and macromolecules *in vivo*, including creatine distribution (*Figure 3*) by targeting its exchangeable amine (NH_2) protons.[98] Unlike CEST, the existing tools to measure Cr or PCr (i.e. ^{1}H- and ^{31}P-MRS) suffer from low sensitivity, limited spatial resolution and partial-volume effect. Furthermore, ^{1}H-MRS only allows total creatine quantification and cannot characterize PCr and Cr individually. Use of CEST, Cr, and PCr can be differentiated as the signals appear at different frequency offset from water (2 ppm and 2.75 ppm, respectively). The advantage of CEST is that the fast exchange acts as a saturation amplifier and is much more sensitive than ^{1}H- and ^{31}P-MRS. CEST however is not as specific since there are other amine exchangeable protons at similar chemical shift offset.[98,99] Haris and colleagues first demonstrated high-resolution mapping of creatine using CEST technique in myocardium of large animal models and in a patient with chronic MI *in vivo*, without the need of exogeneous contrast agent.[98] In a swine model of ischaemia/reperfusion injury, reduced CEST signal in myocardium was consistent with bright region in the LGE images, suggesting reduced metabolic activity.[99] Reduced myocardial creatine CEST contrast was found in obese adults and was inversely correlated with percentage of total body fat, visceral fat mass, and septal wall thickness but uncorrelated to ventricular or contractile function.[100] Prolonged Cr recovery was reported in skeletal muscle of patients with HFpEF, suggestive of impaired PCr regeneration that may contribute to exercise intolerance in HFpEF.[40]

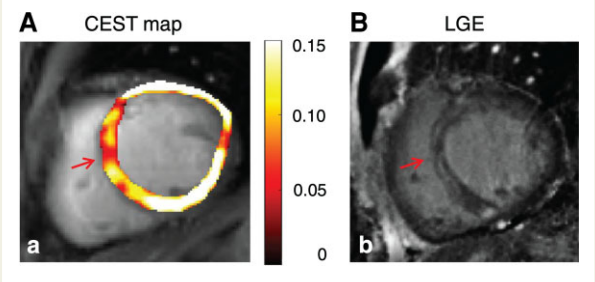


Figure 3 Creatine CEST map and the corresponding LGE image of a patient with chronic MI. The hypointense regions in the CEST maps (*A*) match the LGE positive regions (*B*). LGE, late gadolinium enhancement. Modified from [99], an open-access article under the terms of the Creative Commons Attribution 4.0 International License.

Advantages and limitations

Using CEST technique, chemical property of creatine can be detected with increased sensitivity by a continuous process of re-saturation and exchange. Since CEST imaging relies ultimately on the exchange of protons with the abundant water pool, significantly higher spatial resolution and signal to noise ratio is possible compared with MRS. Lastly, CEST does not require additional specialized coils and a broad band RF power amplifier scanner upgrade since it relies solely on proton signal.

Cardiac imaging using CEST-MRI is prolonged by the necessity of a series of image with multiple acquisition to obtain a full Z-spectrum and to synchronize saturation and acquisition around cardiac and respiratory cycles. Furthermore, CEST requires strong RF saturation pulses that commonly push conventional scanner beyond the safety specific absorption rates limits especially at 3 T. Furthermore, both PCr and Cr have small chemical shifts (~2 ppm) leading to challenges in reduced sensitivity since the high-power RF saturation (3–6 uT) can have a broad bandwidth (1–1.5 ppm) potentially confounding the acquired signal of the exchanged proton. Lastly, CEST contrast depends on both exchange rate, which is pH dependent, and metabolite concentration, both of which may be altered in HF. Separating pH and concentration effects is ultimately required to characterize the underlying pathophysiology but is currently challenging with current cardiac CEST-MRI techniques since scan times would need to be further prolonged.

Major challenges of cardiac metabolic MRI

The main clinical barriers for MRS are centrally focused on technical challenges including specialized hardware requirements,

fundamentally low signal-to-noise (SNR) spectral data and motion correction, and sensitivity to field inhomogeneity. For probing nuclei beyond proton, two key hardware components are needed to realize a MRS acquisition including specialized coils tuned to the frequency of the nuclei of interest and broad band RF power amplifier. Typically, multi-nuclei MR machine and the latter hardware component are quite costly. SNR of MRS spectra relies on the concentration of the nuclei of interest, which for metabolites (~50 mM) is typically 1000x less than water (~55 M).[44,70] Thus, SNR of MRS is much less compared to conventional MRI resulting in lower resolution (~cm) or even single voxel acquisition and dramatically increased scan time (>10 min) due to the need of signal averaging. Motion correction of both cardiac and respiratory motion is ideally needed to avoid partial voluming with the blood pool but given the low spatial resolution (typically large single voxel acquisition) and long scan times, free breathing acquisition is pragmatically employed. MRS is extremely sensitive to magnetic field (B_0) inhomogeneity, which is a common challenge for imaging in the thoracic region. B_0 shimming is requirement for successful MRS and typically necessitates a separate pre-scan of the thoracic cavity and real-time manual calibration of the scanner before each acquisition. In addition, an important consideration for clinical application of hyperpolarized ^{13}C is cost. Clinical polarizer costs almost similar to that of a PET cyclotron and given the cost, clinical usage hyperpolarized ^{13}C is more likely be limited to large academic medical institution.[82]

For CEST, the main clinical barriers are mostly related to prolonged scan times, motion correction, and field inhomogeneity. Because CEST requires multiple measurements at varying chemical shift offsets to reconstruct a z-spectra, it is not possible to acquire under single breath-hold acquisition like conventional parametric mapping. For a single slice, acquisition can vary from 5 min[99] to 30 min [98] depending on how sensitive the CEST technique is the metabolite of interest. Thus, free breathing techniques are required that further the complexity in dealing with motion correction of both respiratory and cardiac motion. Lastly, CEST is sensitive to B_0 and radio frequency field (B_1) inhomogeneity and requires both B_0 shimming and B_1 correction. Consequentially, this can complicate the exam with the need of pre-scans and could significantly prolong scan time further.

The translation to clinical practice will require training for staff members, a dedicated team of basic MR scientists, MR technologist, nurse, and clinicians (radiologist, cardiologist) are typically involved to perform cardiac metabolic MRI.

Concluding remarks and future perspectives

To date, the use of cardiac metabolic MRI (MRS, hyperpolarized MRS and CEST) has been largely limited to research settings (in a single-centre observational study with relatively small study population) and is not routinely used in clinical practice or in multi-centre clinical trials. Nevertheless, the mounting use of CMR in providing a comprehensive assessment of myocardial metabolism in HF is encouraging. Now, the next question that may come in mind is: 'how far have we come? are we any closer to use it in clinical practice?' Unfortunately, the answer is 'we have come far, but we are not quite there yet'. Fortunately, technology for investigation of cardiac metabolism in vivo using cardiac metabolic MRI has evolved, and new MR data acquisition sequences and improved MRI hardware have been developed. Despite the technical feasibility and many advantages of cardiac metabolic MRI, their clinical applications are still in their infancy. Currently, there are several areas that need to be improved to make cardiac metabolic MRI become mainstream procedure in clinical practice.

First, the exact mechanisms linking cardiac metabolic changes to HF development and/or progression are not well understood. Also, there is no universally accepted reference standard to image cardiac metabolism. Thus, standardized acquisition and quantification protocols will have to be implemented and agreed upon to provide clinicians with reliable measurements, which are also comparable among different centres.

Second, the quality cardiac metabolic MRI is highly operator dependent, relying on the proper acquisition and results interpretation by a team who is familiar with the techniques and limitations of cardiac metabolic MRI, making the consistency and reproducibility remain a main challenge.

Third, as the use of cardiac metabolic imaging MRI is still in research phase and has not been implemented in the clinic, often these costs are not covered by health insurance. Correspondingly, the development of new coils and additional specialized software and hardware is less prioritized by the clinical MR company as the market is currently limited to large academic medical institutions.

Nevertheless, cardiac metabolic MRI offers a powerful and versatile tool to probe different aspects of myocardial energy metabolism *in vivo* noninvasively, allowing repeated measurements from the same subjects sequentially or over time. Despite higher costs, limited availability, and the necessities for specialist expertise and dedicated setup, CMR has more advantages when evaluating patients with HF in comparison to other tools, which often require a biopsy of myocardial tissue or the use of ionizing radiation, in providing not only detailed metabolic activities but also additional fundamental information related to diagnosis, disease progression, prognosis, and response to therapy. Yet, investigation and development of the existing and new probes to address the current challenges and limitations must be continued to increase the clinical usefulness. Finally, collaborations among basic research scientist, radiologist, and clinical cardiologist, with strong partnerships between academia, funding agencies, and industry, are needed for the clinical translation from the bench to clinical implementation at the bedside. Cardiac metabolic MRI may have future value in detecting metabolic remodelling in the human heart noninvasively and will be fundamental to the development of drugs aimed at cardiac metabolism in HF.

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