Metabolic and functional evaluation of diabetic cardiomyopathy using MR Spectroscopy and MR Imaging

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Part 1

Technical Advances in MRS and MRI to

Evaluate Diabetic Cardiomyopathy

Chapter 2

Metabolic Imaging of the Human Heart: Clinical Application of Magnetic Resonance Spectroscopy

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Introduction

Cardiovascular MRI has earned its place in the field of clinical cardiac imaging. Regularly used techniques include anatomical imaging, functional imaging, perfusion and delayed enhancement (DE). Cardiac magnetic resonance spectroscopy (MRS) uses the same hardware, measuring the abundance of metabolites in the myocardium in vivo non-invasively without the use of radiation or external tracers. Its main application is currently scientific to gain insight into metabolic changes in cardiac pathologies.

The heart is a metabolically active organ using on average 6 kg of adenosine triphosphate (ATP) each day. As energy is crucial for both systole and diastole, derangements in energy metabolism may be the first step in failure of the heart[1]. By using the gyromagnetic properties of ^{1}H, ^{31}P, ^{13}C and ^{23}Na MRS is a powerful tool to relate energy metabolism to (dys)function of the heart.

The aim of the present review is to provide an overview of the current use, opportunities and limitations of MRS in relation to common cardiac diseases: ischemic heart disease, heart failure, inherited cardiomyopathy, the metabolic syndrome, valvular heart disease and heart transplantation.

Cardiac energy metabolism

A simplified schematic representation of cardiac energy metabolism and opportunities to assess components of metabolism with MRS is depicted in figure 1. On average, the heart cycles 10 tons of blood each day in 100.000 heart beats. To meet the enormous ATP requirement, cardiomyocytes fuel themselves with free fatty acids (FFA) and glucose as the primary source of chemical energy. FFA and glucose contribute to ATP synthesis in terms of supply of chemical energy in a ratio of 3:1 in normal situations. Derangements in substrate utilization are associated with a wide variety of diseases which will be discussed below. The uptake of FFA by the fatty acid transporter is an energy-consuming process. Fatty acids enter the mitochondrion where beta-oxidation takes place after which the intermediate Acetyl-Coenzyme A (CoA) enters the Krebs cycle. The uptake of glucose by the glucose transporter type 4

(GLUT4) is insulin-dependent. Glucose is converted to pyruvate in the cytoplasm by glycolysis. Pyruvate enters the Krebs cycle in the mitochondrion (figure 1).

The process of oxidative phosphorylation is the basis for production of energy by the mitochondrial respiratory chain. This yields energy needed for the generation of ATP from adenosine diphosphate (ADP). Transfer of chemical energy (ATP) from mitochondrion to myofibril is provided by the creatine kinase energy shuttle. In the mitochondrion, creatine kinase catalyses conversion of ATP and creatine to phosphocreatine (PCr) and ADP (figure 1). PCr rapidly diffuses to the myofibrils. Once arrived there, creatine kinase catalyses the reaction back to ATP and free creatine. Creatine then diffuses back to the mitochondrion. Two thirds of the total creatine pool is phosphorylated to PCr; the other part remains in the cell as free creatine. The creatine kinase system acts as an important energy buffer, providing the heart of energy when the demand outweighs the supply. Such situation results in a decreased PCr level and increased ADP level whereas ATP levels are held constant. Overconsumption of PCr and subsequent increase in ADP lead to inhibition of many intracellular enzymes[1]. Furthermore the process of energy production is regulated by calcium flux. For example calcium flux from the sarcoplasmic reticulum to the mitochondrion can directly activate oxidative metabolism[2]. Both diastolic and systolic heart function are dependent upon energy synthesis and utilization. This is reflected by the fact that calcium-handling is an important determinant of ATP-consuming relaxation of cardiomyocytes as well as systolic function of the heart[3].

Metabolic assessment of the myocardium with ^{1}H, ^{31}P, ^{13}C and ^{23}Na - MRS

MRS of the heart has been performed using 1.5 and 3.0 tesla (T) MR systems, and recently even using ultra-high 7T MR systems. Modern systems can be delivered with software to support MRS. Depending on the MR system (manufacturer, field strength) coils for ^{1}H and ^{31}P spectroscopy are commercially available. However to initiate cardiac MRS technical development and support is needed to optimize i.e. shimming techniques, gradients and pulse sequences. Furthermore, each MR system

requires its own specific adjustments. For ^{13}C and ^{23}Na-MRS coils, pulse sequences and metabolic tracers are not routinely obtainable.

As the heart moves due to contraction and breathing, MRS is subject to motion artifacts. Therefore, ECG-triggering is necessary to correct for motion of the heart throughout the cardiac cycle. Respiratory motion compensation has been performed with respirometer-triggered acquisition, breath-hold scanning sequences and by using navigator echoes[4,5]. Figure 2 shows a navigator-gated acquisition of a ^{1}H spectrum of the heart. The scanning time for ^{1}H-MRS varies from a single breath-hold to twenty minutes (excluding time required for ^{1}H imaging for planning of the voxel). The most commonly used pulse sequences are Stimulated Echo Acquisition Mode (STEAM) and Point Resolved Spectroscopy (PRESS). STEAM has the disadvantage of a lower signal-to-noise ratio (SNR) and increased susceptibility to motion, but enables acquisition with shorter echo time and hence better detection of fat. As SNR increases with field strength ^{1}H-MRS has recently been performed in one breath-hold at 3T with STEAM[5]. Based on the required variability in the measurement, mode of respiratory compensation and scanning time an appropriate method can be chosen. ^{31}P-MRS using the method depicted in figure 3 requires roundabout ten minutes. For postprocessing the spectra jMRUI is the most commonly used program. Table 1 shows an overview of the potential clinical applications of ^{1}H, ^{31}P, ^{13}C and ^{23}Na-MRS and challenges of the technique.

^{1}H is the most suitable nucleus for MRS because it has the highest MR sensitivity. ^{1}H-MRS can detect various metabolites in the myocardium that are associated with (dys)function (see figure 1). Assessment of triglyceride (TG) content of the myocardium is of major importance in view of the epidemic proportions of cardiovascular disease related to obesity in modern society. Using ^{1}H-MRS myocardial TG content has been shown to be an independent predictor of diastolic dysfunction in both healthy men[6] and type 2 diabetes mellitus (T2DM) patients[7]. Furthermore, creatine content can be determined with ^{1}H-MRS. As part of the creatine kinase energy shuttle, creatine content reflects the energy status of the heart. In heart failure and non-viable myocardium creatine content is depleted[8,9]. Other metabolites that can be detected are lactate, (de)oxymyoglobin and carnitine.

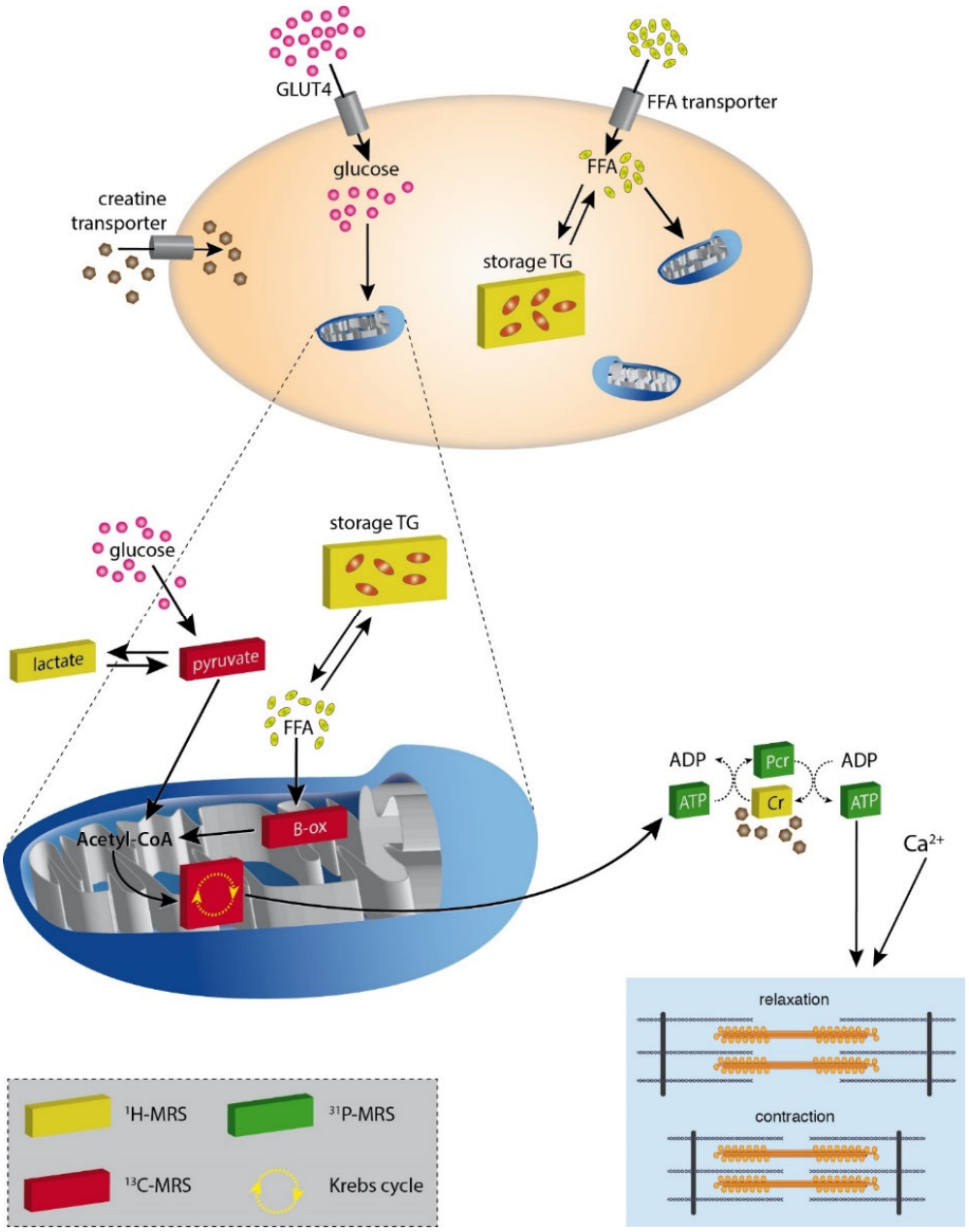

Figure 1 Magnetic resonance spectroscopy (MRS) assessment of cardiac energy metabolism. Upper figure depicts a schematic diagram of energy metabolism of the cardiomyocyte. In the mitochondrion (blue) ATP is generated from mainly glucose and FFAs. ATP and regulation by calcium flux are needed for contraction and relaxation of the myofibrils. The coloured boxes (yellow, green and red) indicate opportunities for measurement with MRS, respectively ^{1}H, ^{31}P, and ^{13}C. Glucose and FFAs are the primary sources of chemical energy. Glucose uptake by the GLUT4 is insulin dependent; FFAs are transported into the cell via the FFA transporter. Glucose is subject to glycolysis and converted to pyruvate which enters the mitochondrion or is converted to lactate. FFAs are either stored as triglycerides or enter the mitochondrion. Both pyruvate and FFA (after β-oxidation) give rise to acetyl-CoA. Acetyl-CoA enters the Krebs cycle. In the mitochondrion the process of oxidative phosphorylation generates ATP. Outside the mitochondrion energy is transferred to PCr which releases its energy in the myofibrils giving rise to ATP and Cr. Acetyl-CoA, acetyl-coenzyme A; ADP, adenosine diphosphate; ATP, adenosine triphosphate; B-ox, β-oxidation; Ca^{2+}, ionised calcium; Cr, creatine; FFA, free fatty acid; GLUT4, glucose transporter type 4; PCr, phosphocreatine; TG, triglyceride content.

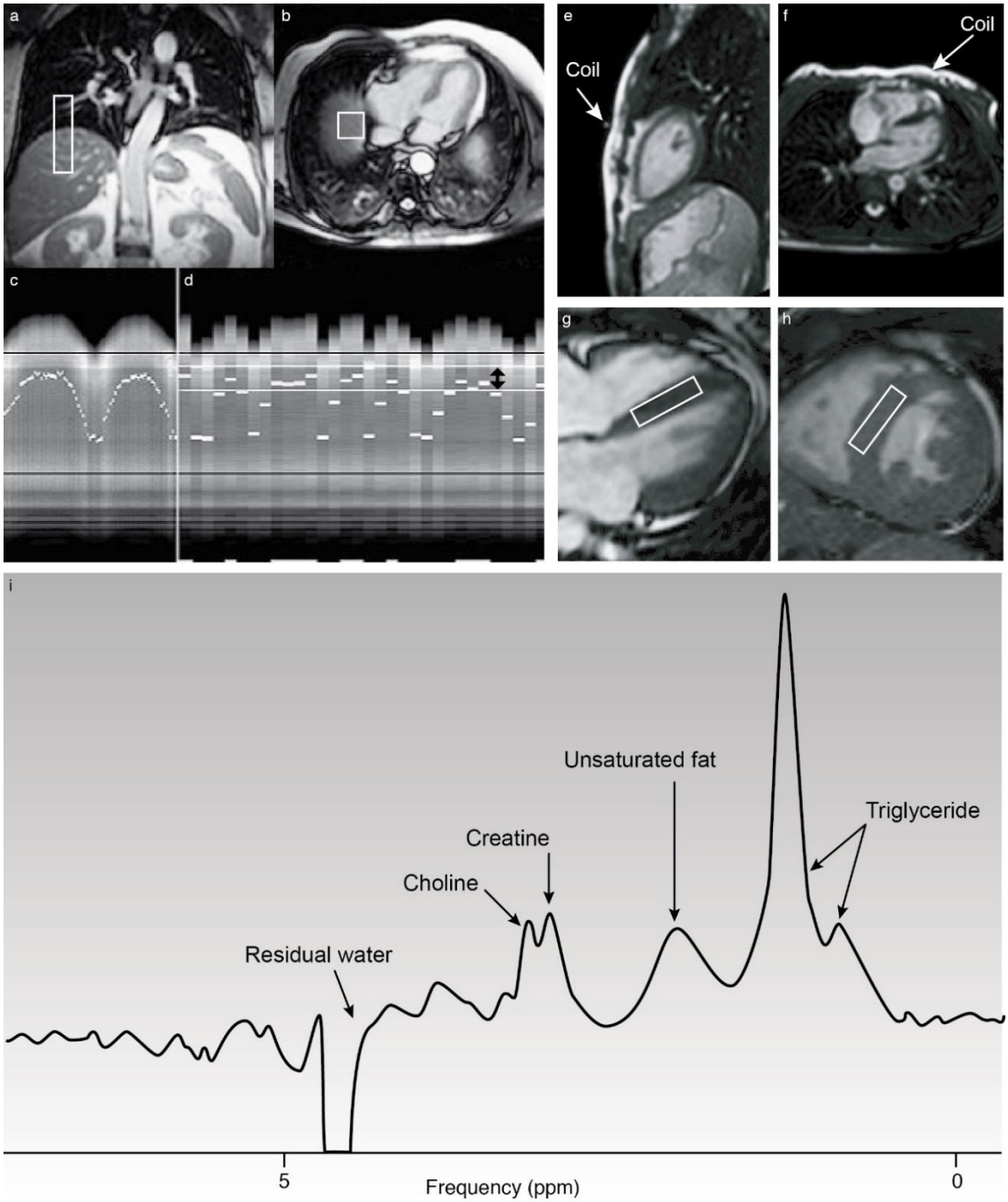

Figure 2 Navigator gated ^{1}H magnetic resonance (MR) spectroscopy of the heart. Upper left panel shows preparation and monitoring of the respiratory navigator gating technique. A pencil beam is placed on the dome of the right hemidiaphragm on coronal (A) and transverse (B) MR images. White dots (C) represent the automatically traced position of the diaphragm during calibration. In (D) horizontal lines indicate the acceptance window; whenever the detected position of the diaphragm is within the predefined window, the spectroscopic measurement is stored. The upper right panel shows the acquisition of the spectrum. The surface coil is positioned just below the anatomical level of the mitral valve on sagittal (E) and transverse (F) MR images. By using a four chamber (G) and short axis (H) view the spectroscopic volume is placed in the interventricular septum. As water is by far the most abundant substance, an ^{1}H spectrum as depicted in (I) can only be acquired after applying suppression of the water signal. Adapted from van der Meer et al.[4]

Table 1. Summary of potential clinical applications of cardiac MRS

Nucleus	Metabolites	Potential clinical application	Technical hurdles
^{1}H	Creatine content	Heart Failure, determination of myocardial viability	- Need to suppress water signal - Need to compensate breathing artifacts - Improved spatial resolution required
	Triglyceride content	Obesity / Metabolic syndrome / DM2: myocardial triglyceride content	
^{31}P	PCr	Detection of ischemia, scar tissue, heart failure	- Very low spatial resolution
	ATP	Detection of scar tissue	
	PCr/ATP ratio	Decreased in: - ischemic heart disease - heart failure - valvular disease - DCM - HCM - Diabetic cardiomyopathy	
^{13}C	1-^{13}C pyruvate: alanine, lactate, bicarbonate, pyruvate dehydrogenase flux	Ischemic heart disease, viability assessment, heart failure, diabetic and inherited cardiomyopathy	- Complex technique to generate hyperpolarized ^{13}C - Expensive
	2-^{13}C-pyruvate: downstream metabolites of Acetyl-CoA (Krebs cycle and Acetyl carnitine)	Heart failure, inherited cardiomyopathy	
	^{13}C-bicarbonate: intracellular pH	Ischemic heart disease, heart failure, heritable metabolic cardiomyopathy	
^{23}Na	Sodium content	Scar tissue Ischemia Hibernating myocardium?	- Low spatial resolution - No absolute quantification of sodium possible

^{31}P-MRS has been used extensively to assess high energy phosphate metabolism which is crucial for maintaining normal function of the heart. ^{31}P-MRS is therefore a useful tool to analyze the energy status of myocardium. The PCr peak and a combination of the three peaks of ATP are used to calculate the PCr/ATP-ratio (see

figure 1). This ratio is the most commonly used parameter in ^{31}P-MRS of the heart. In general there are two conditions associated with a decreased ratio: 1. ATP synthesis cannot meet the ATP requirement i.e. in ischemia; 2. Decreased total creatine supply is diminished. Absolute measurements of PCr and ATP can also be assessed albeit in a more complex way[1]. Figure 3 shows an example of a technique to perform ^{31}P-MRS of the heart and an example of a phosphorus spectrum.

^{13}C-MRS is limited by the fact that it has too low MR sensitivity and abundance in myocardial tissue to be used in vivo. However, with the exciting new technique of hyperpolarization (dynamic nuclear polarization technique) the signal can be increased > 10.000 times. A hyperpolarized metabolic tracer is made by mixing the molecule with free radicals, placement in a magnetic field and then freezing it to a temperature close to 1K[10]. In cardiometabolic research, $^{1-13}$C pyruvate, $^{2-13}$C pyruvate and ^{13}C-bicarbonate tracers have been used in animal studies allowing analysis of pyruvate dehydrogenase flux and assessment of components of beta-oxidation and Krebs cycle (see figure 1). Figure 4 shows that ^{13}C-MRS could be used for detection of ischemia and / or infarction. Although $^{1-13}$C pyruvate has been used in research setting in one human study, technical issues regarding safety have to be addressed before the technique of hyperpolarization gains regulatory approval for widespread use.

^{23}Na-MRS can be used to produce images based on the level of sodium content of the myocardium. The regional spectra can be converted into signals producing an MR image of the myocardium, based on sodium content. As the sodium content alters in ischemic and infarcted tissue, ^{23}Na MRI can be used to detect myocardial infarction and viability[11,12].

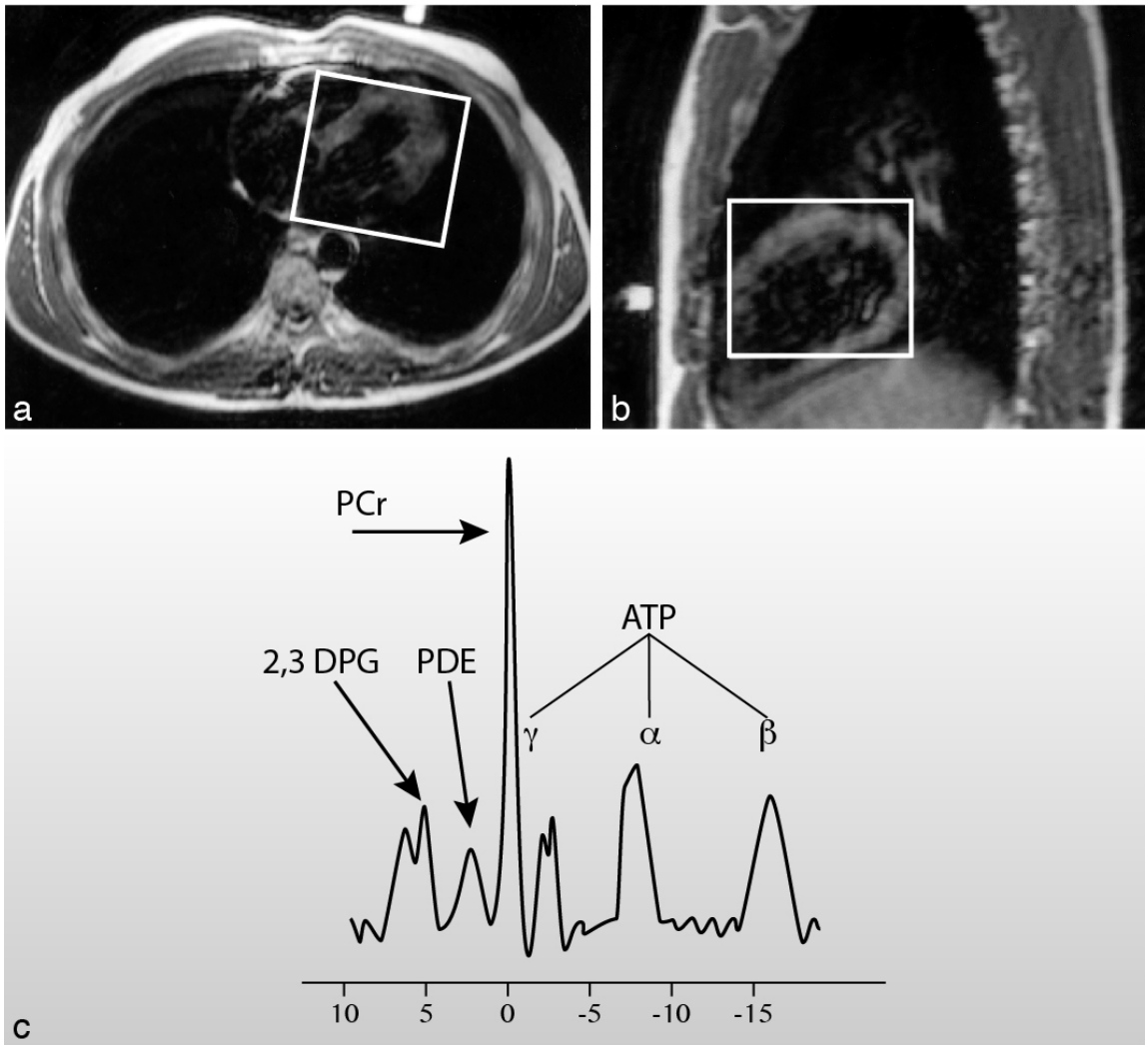

Figure 3 ^{31}P-magnetic resonance spectroscopy of the human heart. Volume of interest is positioned in an optimal orientation relative to the left ventricle based on scout images in the transverse (A) and sagittal imaging plane (B). The volume (square box) is placed perpendicular to the chest wall to prevent contamination with skeletal muscle. By adjusting the level of the volume selection in the caudo-cranial direction, contamination of the sensitive volumes by diaphragm muscle and liver tissue can be prevented (B). The white square on the chest wall originates from a reference sample in the centre of the surface coil. With this technique a spectrum as shown in (C) can be acquired. Note that with this technique no regional differences can be detected, but an average of the signals in the left ventricle is acquired. 2,3 DPG, 2,3-diphosphoglycerate; PDE, phosphodiesters; PCr, phosphocreatine.

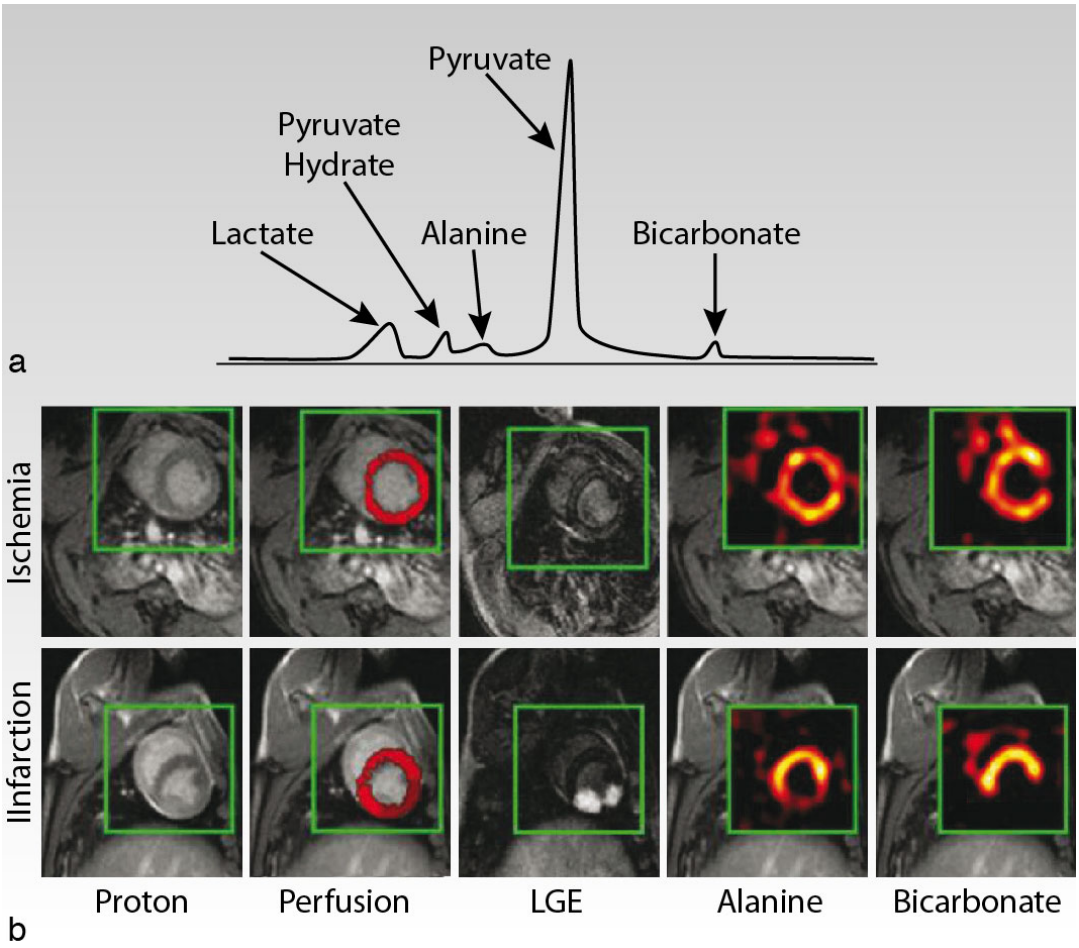

Figure 4 ^{13}C-magnetic resonance spectroscopy (MRS) combined with MRI of a pig heart. By combining proton MRI, perfusion and late gadolinium enhancement (LGE) with ^{13}C MRS with a $^{1\text{-}13}$C pyruvate tracer, ischaemic and infarcted tissue can be characterised. These images were obtained in pig hearts. By superimposing the signals acquired in spectroscopy on proton MR images, maps can be made for different metabolites. Alanine reflects cytoplasmic cell metabolism whereas bicarbonate indicates mitochondrial activity. In the ischaemic model (15 min occlusion of left circumflex artery) only the bicarbonate changes, whereas in the infarction model (45 min of occlusion) the alanine signal drops and the bicarbonate signal almost disappears, spatially correlated to LGE area. Note that the spatial resolution is high enough to establish regional differences in intensity. Adapted from Golman et al.[23]

Ischemic heart disease

Ischemic heart disease develops when oxygen demands outweigh the supply. In daily practice, coronary angiography (CAG) or coronary artery CT are the standard procedures to rule out significant obstructive coronary artery disease (CAD). However, ischemia can also occur without significant stenosis. The cause of ischemia in the absence of significant CAD may be microvascular disease and is associated with a worse prognosis in terms of survival and reinfarction[13]. Furthermore, the discrimination between non-viable (scarred) and viable (hibernating or stunned)

myocardium is of clinical importance to determine the potential benefit of revascularization.

Since oxygen is crucial for the mitochondrial process of oxidative phosphorylation, ischemic myocardium is largely dependent on inefficient anaerobic glycolysis for the production of ATP. In ischemic myocardium ATP production, and thus formation of PCr decreases. A decrease in the PCr/ATP ratio reflects exhaustion of energy reserves of the myocardium.

^{31}P-MRS has been used in extension to investigate cardiac energy metabolism in ischemic and infarcted tissue. Weiss et.al. performed a study in patients with > 70% stenosis of the left anterior descending coronary artery (LAD) before and after revascularization. Myocardial ischemia was provoked by handgrip exercise. Patients with stenosis of the LAD had a significantly decreased PCr/ATP-ratio during exercise whilst no difference between cases and controls could be established in rest. After revascularization the 'between group' and 'within group' difference was recovered[14]. An interesting finding was that in women admitted with chest pain with normal CAG, 7 out of 35 had an abnormal PCr/ATP ratio during handgrip exercise[15]. To evaluate the prognostic finding of an abnormal PCr/ATP ratio, a prospective follow up study was performed in women with chest pain, normal CAG with or without abnormal PCr/ATP ratio and a reference group of 352 women with known coronary artery disease. After adjusting for CAD and cardiac risk factors, a PCr/ATP ratio decrease of 1% increased the risk for cardiovascular events by 4%[15,16]. The most likely explanation for these findings is that patients with normal CAG and abnormal ^{31}P-MRS suffer from microvascular pathology.

Opposed to viable myocardial tissue, the PCr/ATP ratio is not useful in infarcted tissue since both PCr and ATP levels are reduced[17]. However, absolute levels of PCr and ATP do correlate with infarct size and viability respectively. In a study in humans with either a fixed or reversible defect on 201TI scan, myocardial PCr content decreased significantly in patients with reversible and fixed defects when compared to healthy controls. ATP content decreased significantly in subjects with fixed defects, but did not in those with reversible defects[18]. These data suggest that ^{31}P-MRS could be used to determine myocardial viability. Moreover, in a rat model of myocardial

infarction, whole-heart PCr content was inversely correlated with infarct size, whereas ATP distribution provides a profile of viable myocardium around the infarction reflecting remodeling of the heart[19].

In rats that underwent ligation of the LAD, ^{1}H-MRS proved lower creatine content as compared to controls[20]. In line with this, in humans total creatine content was significantly lower in regions of infarction[8].

In animal studies it has been shown that viable and nonviable myocardium have a different sodium content as detected by ^{23}Na-MRI. ^{23}Na signal intensity (SI) is elevated in acute ischemia and remains increased afterwards in humans[21]. To further investigate the role of ^{23}Na-MR imaging in ischemic heart disease, ^{23}Na-MRI was compared with cine MR imaging and delayed enhancement (DE) imaging in 15 patients with subacute infarction and 15 with chronic infarction. In subacute infarction all patients showed regional elevated ^{23}Na SI that correlated well with wall motion abnormality (WMA) and with DE (r = 0.68). In chronic infarction, the patients that had presented with WMA showed increased ^{23}Na SI even in cases without DE, indicating that ^{23}Na MRI could detect hibernating myocardial tissue[22].

As shown in figure 4 ^{13}C-MRS has the potential to distinct between viable and non-viable myocardial tissue in an experiment in pigs[23]. However this technique has not been performed in cardiovascular research in humans as yet.

A major drawback of application of MRS in general, although significant in ischemic heart disease, is the low spatial resolution. Since ischemic heart disease does not involve the whole myocardium, information on localization of the ischemic or infarcted area is hard to establish with the current techniques. Overcoming these issues with for example higher field imaging or hyperpolarization could pave the way for MRS to be of diagnostic relevance, most notably in patients with suspected ischemic heart disease without coronary artery stenosis on CAG. Moreover, MRS could be of use in patients to discriminate between viable and non-viable myocardium.

Heart failure

Heart failure is the final common pathway of a diverse set of specific diseases which will be described in this section. Heart failure in general, its prognosis and the

effect of (non-) pharmacologic interventions have been studied with MRS. The most commonly studied causes of heart failure are dilated cardiomyopathy, hypertrophic cardiomyopathy and cardiomyopathy related to the metabolic syndrome and T2DM. Metabolic imaging in heart failure has generally focused on two aspects: 1) high energy phosphate metabolism (^{31}P) and 2) substrate utilization and myocardial triglyceride content (^{1}H).

Decreased ATP metabolism is the final common pathway in heart failure and can be measured by ^{31}P-MRS. Both the absolute level of ATP and ATP flux are diminished[24,25]. The PCr/ATP ratio may underestimate the metabolic derangement because both PCr and ATP levels are decreased[26].

The causality between altered substrate preference (FFA vs glucose) and heart failure is controversial and beyond the scope of this review. To summarize clinically relevant findings:

- High levels of circulating FFA's are related to cardiac lipotoxicity and reduce cardiac glucose utilization[27].
- In advanced heart failure systemic and cardiac insulin resistance are related to myocardial lipotoxicity irrespective of the presence of obesity[28].
- Therapeutic interventions in substrate utilization can improve heart function. For example, inhibition of fatty acid oxidation and stimulation of glucose use with trimetazidine improved the PCr/ATP ratio and cardiac function in heart failure patients[29].

Dilated cardiomyopathy

Dilated cardiomyopathy is characterized by left ventricular dilatation, myocardial wall thinning and decreased systolic function. Underlying mechanisms are cardiomyocyte death and myocardial fibrosis caused by a heterogeneous group of mutations in different pathways[30]. These mechanisms reflect global cardiac metabolic changes, allowing regional spectroscopy techniques to be representative of energy metabolism in the whole heart. MRS has provided insight into metabolism of cardiomyocytes in DCM. The severity of dilated cardiomyopathy in terms of LV end-diastolic wall thickness and ejection fraction showed a linear regression with the PCr/ATP ratio[31]. Whether metabolic derangements precede heart failure and play a

role in the etiology, or it merely is an innocent bystander, could not be extracted from this observational study. There are however indications that alterations in the high energy phosphate metabolism play an important role in the pathogenesis of dilated cardiomyopathy. First, in patients with dilated cardiomyopathy a decreased PCr/ATP-ratio has been shown to be an independent predictor of both total and cardiovascular mortality and offered significant independent prognostic information when compared to NYHA class[32]. Second, in patients and carriers with Duchenne or Becker muscular dystrophy (the Xp21 dystrophies) the reduced PCr/ATP ratio's were not associated with LV mass or ejection fraction. As patients and carriers of the Xp21 dystrophies frequently develop cardiac hypertrophy and dilated cardiomyopathy, this study suggests that the metabolic derangement precedes cardiac structural changes and failure[33] . Moreover, diuretics and ACE-inhibitors induce an improvement in the PCr/ATP ratio parallel to clinical improvement, suggesting that MRS could be used as a quantitative marker of success of therapy[34]. In the future ^{13}C-MRS might be used to unravel the causality between substrate use and heart failure as shown in an experimental model of pigs with DCM[35].

Hypertrophic cardiomyopathy

Cardiac hypertrophy has different etiologies. It can be caused by genetic factors (hypertrophic cardiomyopathy), may be the result of chronic hypertension and is also seen physiologically in athletes. Metabolism in these different hypertrophic hearts has been studied predominantly with ^{31}P-MRS. In hypertrophic cardiomyopathy a reduced PCr/ATP ratio has been a consistent finding, in the context of hypertension[36], as well as in young asymptomatic HCM patients[37]. On the contrary, there is a normal PCr/ATP ratio in physiologic hypertrophy[38]. The fact that a reduced PCr/ATP ratio precedes the symptomatology of HCM patients, suggests a causative role for metabolic derangement in HCM. Further evidence of this is that patients with a genetic hypertrophic cardiomyopathy due to sarcomeric gene mutations, the metabolic derangement was not correlated with the degree of hypertrophy[39]. This study therefore suggests that 30% decrease in the PCr/ATP ratio is not a consequence of hypertrophy / heart failure / strain but may be at the beginning of the pathophysiological process. The fact that energy deficiency is at least in part

responsible for heart failure was generated by a study by Abozguia et.al. They proved in a placebo-controlled RCT that the PCr/ATP ratio increased with perhexiline, an agent thought to improve cardiac energetics by providing a shift from fatty acid oxidation to glucose utilization. The increased PCr/ATP ratio was associated with an increase in exercise capacity and improvement in diastolic function[39,40]. ^{31}P-MRS has the potential to play a role in determining prognosis of patients with HCM and support intervention trials focused on the potential of improving energy metabolism to ameliorate cardiac function.

Metabolic syndrome

Apart from an increased risk of coronary events, patients with the metabolic syndrome (including T2DM) have an increased risk of developing heart failure without evidence of ischemia / infarction, the so called diabetic cardiomyopathy. The pathophysiology of cardiac dysfunction in the metabolic syndrome is rather complex and reviewed by van der Meer et.al.[41]. It appears that cardiac energy metabolism plays a crucial role in diastolic and systolic dysfunction in these patients. Cardiac energy metabolism in the metabolic syndrome is characterized by an increase of fatty acid uptake and oxidation becomes less efficient[27]. Consistent with this hypothesis, the PCr/ATP ratio was inversely correlated to fasting FFA concentrations in T2DM patients whilst the PCr/ATP ratio was lower compared to healthy controls, despite the fact that cardiac mass and function appeared to be normal[42]. Accumulation of triglycerides (as detected by ^{1}H-MRS) in the heart could play a role in the pathogenesis of heart failure in patients with obesity and / or diabetes. There is profound evidence that myocardial triglycerides reflect cardiomyocyte function by a process called lipotoxicity: the accumulation of toxic lipids such as diacylglycerol and ceramide[28,43]. Indeed myocardial triglyceride content has been shown to be an independent predictor of diastolic dysfunction[3]. Interestingly diastolic dysfunction can be reversed, in parallel with decreased myocardial steatosis, by prolonged caloric restriction in T2DM patients[44]. Another study with T2DM patients has proven that a short term increment of FFA flux induced by fasting, is associated with myocardial steatosis and diastolic dysfunction[45]. However, in morbidly obese patients undergoing bariatric surgery, the improvement of diastolic function after six months was not associated with a change

in myocardial triglyceride content[46]. ^{1}H-MRS and ^{31}P-MRS were also used to investigate the mechanism of improvement of cardiac function by pioglitazone. Here, the functional improvement was not associated with metabolic changes[47]. In the future MRS could be helpful to unravel pathophysiology of cardiovascular disease in the metabolic syndrome, and aid in the evaluation of the effect of life style and / or pharmacologic interventions, especially when combined with cardiovascular magnetic resonance imaging. ^{13}C-MRS could help to study the complex interplay between substrate use and heart failure in patients with the metabolic syndrome / diabetic cardiomyopathy[48].

Valvular heart disease

In valvular heart disease the timing of valve replacement is an important issue: a balanced decision must be taken on the basis of expected benefits versus the risk related to the replacement procedure. Studies involving ^{31}P-MRS of the heart have been performed in patients with aortic stenosis (AoS), aortic incompetence (AoI) and mitral regurgitation (MR). In line with observations in patients with heart failure, the PCr/ATP ratio was reduced in AoS and AoI patients with symptoms of heart failure when compared to asymptomatic patients[49]. A similar study performed by Neubauer et. al. concordantly showed a decreased ratio only in patients with NYHA class 3 or 4. The ratio was more disturbed in AoS patients with the highest wall stress[50]. In 22 patients with MR the PCr/ATP ratio was higher in those with symptoms and more severe disease. Again, there was a correlation between the PCr/ATP ratio and various parameters of ventricular dysfunction. In this study there was no correlation with wall stress however[51]. Breyerbacht et.al. performed ^{31}P-MRS before and 40 weeks after aortic valve replacement in 9 AoS patients. PCr/ATP ratio's improved significantly from 1,28 to 1,47[52]. The fact that the PCr/ATP ratio is a marker of disease severity in valvular heart disease and is an independent predictor of mortality in DCM, suggests that serial ^{31}P- MRS assessments in patients with valvular heart disease could prove to play a role in the timing of a surgical procedure. However further studies are needed in that respect. In the research setting, MRS could aid to unravel the causal relationship between impaired cardiac energy metabolism and mechanical changes: how do they interact to ultimately result in a failing heart?

Heart transplantation

Cardiac allograft patients are at risk for rejection. The golden standard to diagnose rejection is based on histology of the myocardium which warrants repeated biopsy procedures in the post-transplant period[53]. Therefore a non-invasive tool for this diagnosis is desirable. To investigate the sensitivity of MRS in predicting rejection, ^{31}P-MRS at rest was performed in 14 patients and 17 healthy controls late after transplantation (months to years). The PCr/ATP ratio was significantly lower in transplant recipients than healthy controls. However ^{31}P-MRS could not reliably predict in which patients augmented immunosuppressive therapy was warranted[54]. Van Dobbenburgh et al. performed a similar study but assessed ^{31}P-MRS repeatedly in the early post-transplant period to investigate whether ^{31}P-MRS could detect early acute rejection. Again PCr/ATP-ratio's were lower in heart transplant recipients than controls, with the ratio recovering in time. However, no correlation was found between PCr/ATP ratio's and biopsy scores of rejection: ^{31}P-MRS was unable to predict early acute rejection[55]. Evanochko et.al. performed a ^{31}P-MRS stress test in heart transplant recipients with normal CAG. Interestingly 10 out of 25 had a positive stress test with a mean decrease of the PCr/ATP ratio of 25,6 ± 3.6%. Further research is needed to determine the cause of this finding. A possible explanation could be that the reduced ratio is an early sign of chronic allograft vasculopathy[56]. These findings are hopeful with respect to implementing MRS techniques in the follow-up of heart transplant patients, although the exact role of MRS remains to be established.

Future direction

The fact that function of the heart depends on myocardial energy metabolism makes MRS an excellent technique to evaluate diseased myocardium. However, the low spectral and temporal resolution combined with the lack of availability of MRS to study the heart in most clinics hampers widespread use clinical cardiology. Moreover, the currently used techniques remain time consuming.

Whether cardiac spectroscopy will aid in diagnostic and therapeutic decision making depends on the achievement of better spatial and temporal resolution as well

as reproducibility. There are various technical opportunities to achieve this goal. First of all, by using higher field MR systems (> 3 Tesla), the advantage of increased SNR could result in better resolution and reproducibility[57]. Furthermore, development of improved shimming algorithms, pulse sequences and receiver coils could aid in achieving higher spatial resolution MRS, i.e. to be able to perform an MRS-based analysis in line with the 17-segment model for detection of regional metabolic alterations specific for (non) viable myocardium. One of the most promising new techniques is hyperpolarization. Hyperpolarized ^{13}C with various tracers can assess substrate flux and thereby gain a position in clinical practice[48,58].

Conclusion

Magnetic resonance spectroscopy is a unique non-invasive, non-irradiating tool to assess cardiac metabolism in humans. In research setting, MRS has provided insight into pathophysiology of multiple cardiac diseases. The tight relation between energy metabolism and cardiac function potentiates spectroscopy to be of use in diagnostics, prognosis and treatment guidance in cardiology practice. Continuous improvements regarding technical optimization, and exciting new techniques such as hyperpolarization, may help to implement cardiac MRS in selected patients in daily practice.

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