

Metabolic imaging in dilated cardiomyopathy

Stefan Neubauer

University of Oxford Centre for Clinical Magnetic Resonance Research, Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford, United Kingdom

Correspondence: Professor Stefan Neubauer, Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford OX3 9DU, UK.

Tel: +44 0 1865 851085; fax: +44 0 1865 222077; e-mail: Stefan.neubauer@cardiov.ox.ac.uk

Sponsorship: The author is funded by the British Heart Foundation, the Medical Research Council, the Wellcome Trust, and the National Institute for Health Research Biomedical Research Centre Programme.

Abstract

Cardiac metabolism is deranged in dilated cardiomyopathy (DCM). Phosphorus-31 (^{31}P) and hydrogen-1 (^1H) magnetic resonance spectroscopy (MRS) allow for the non-invasive assessment of various aspects of cardiac metabolism, showing deranged cardiac energetics and lipid accumulation in DCM. In the future, MRS may become an important biomarker tool for monitoring the effects of novel heart-failure treatments in DCM.

■ *Heart Metab.* 2011;49:13–16.

Keywords: Dilated cardiomyopathy, energetics, magnetic resonance spectroscopy, metabolism, steatosis

Introduction

Dilated cardiomyopathy (DCM) is a common cause of heart failure, and may be due to many different etiologies (genetic, post myocarditis, toxic, etc.). A common feature of DCM is a derangement of cardiac metabolism. As reviewed elsewhere, metabolic alterations are likely to be a key factor in the pathophysiology of contractile dysfunction [1]. Accordingly, metabolic modulation currently appears as one of the most promising new strategies for chronic drug therapy with the potential to further improve long-term prognosis, as an additive to established therapy with angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and diuretics.

In light of this, non-invasive assessment of the metabolic state of the myocardium in DCM has been an important goal in cardiology for many decades. In principle, two techniques allow for this: magnetic resonance spectroscopy (MRS) and positron emission tomography (PET). The largest number of studies has

been performed with MRS [2], and early proof-of-principle investigations point to the value of metabolic MRS parameters as biomarkers of disease and prognosis, and for monitoring therapy.

Methodological considerations

MRS can be performed on the same magnetic resonance systems used for imaging, typically at a field strength of 1.5–3 tesla (T). There are, however, additional hardware and software requirements, such as a phosphorus-31 (^{31}P) surface coil, a broadband radiofrequency transmitter, spectroscopy pulse sequences, and post-processing software [2,3]. After shimming the magnetic field, an MR spectrum is obtained using a spectral localization technique, which makes it possible to obtain signal from a voxel element within the heart [2]. Because of the inherent low resolution of MRS, a large number of acquisitions have to be signal averaged in order to obtain a

Metabolic imaging

Stefan Neubauer

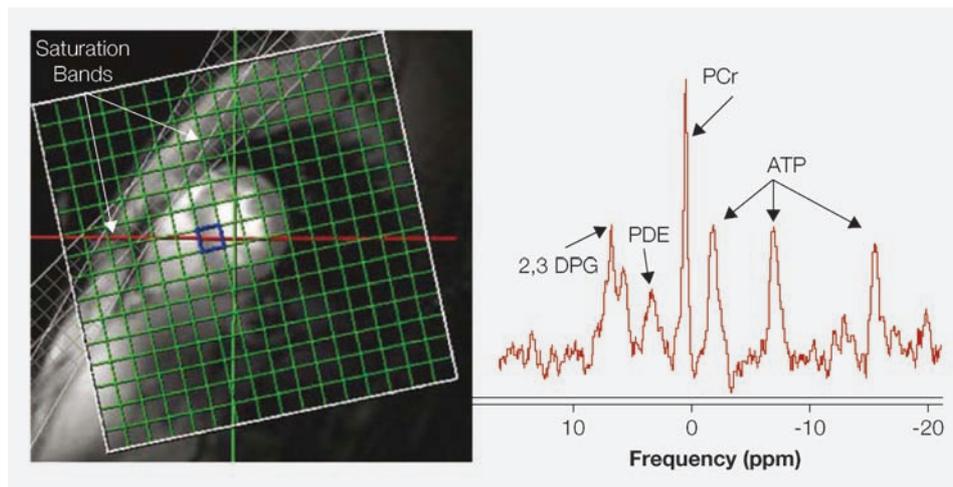


Figure 1. In vivo human cardiac phosphorus-31 (^{31}P) magnetic resonance spectroscopy, 3-dimensional chemical shift imaging sequence. Left: Short-axis hydrogen-1 (^1H) magnetic resonance image of the heart with a superimposed grid of spectroscopic voxels. The interrogated cardiac voxel (blue square) is placed in the interventricular septum to avoid contamination from skeletal muscle. Saturation bands are placed over the chest wall skeletal muscle to suppress further any skeletal muscle signal. Right: Example of a cardiac ^{31}P magnetic resonance spectrum in a healthy individual. Resonances for 2,3-diphosphoglycerate (2,3-DGP), phosphodiester (PDE), phosphocreatine (PCr), and the three phosphorus atoms of adenosine-5'-triphosphate (ATP) (from left to right: γ , α , and β ATP) are detectable. 3T Siemens TIM-Trio system. Acquisition matrix size 16x16x8 voxels, field of view 240 × 240 × 200 mm. Reprinted from [16].

magnetic resonance spectrum with an acceptable signal-to-noise ratio. A typical ^{31}P spectrum from a normal individual is shown in Figure 1 (Figure 1). Resonances are shown for the three phosphorus atoms of adenosine-5'-triphosphate (ATP) (α , β and γ ATP), phosphocreatine (PCr), and also 2,3-diphosphoglycerate (2,3-DPG) from blood and phosphodiester (PDE) from phospholipids. The PCr to ATP ratio is an exquisitely sensitive index of the energetic state of the heart

[4]. Figure 2 shows a hydrogen-1 (^1H) MR spectrum from the heart (Figure 2). While ^1H spectra show many metabolites, quantification has so far been limited to lipids (triglycerides), which provide a measure of myocardial steatosis (another key factor in the development of contractile dysfunction), and to the total creatine peak [5].

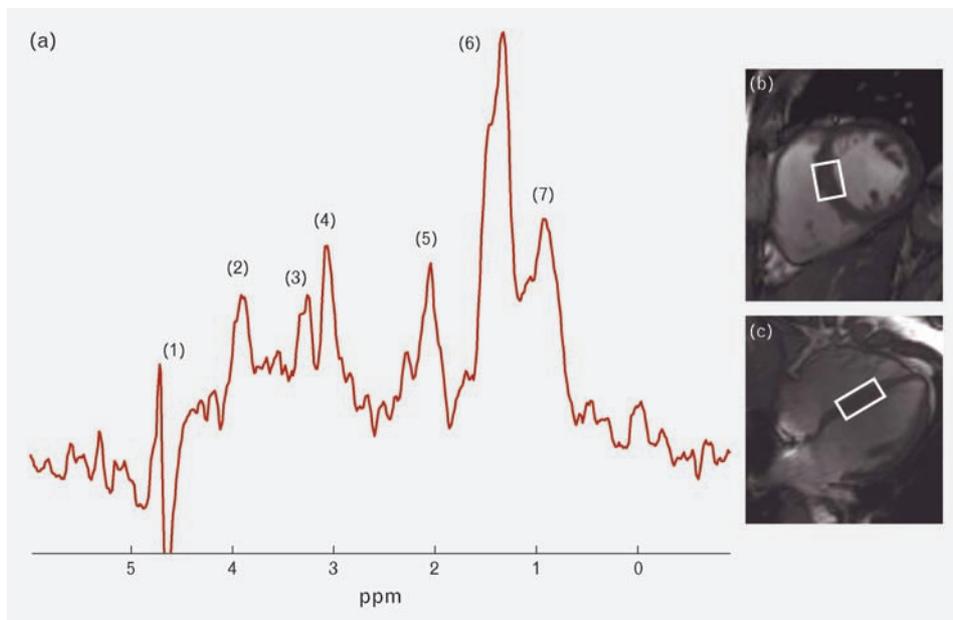


Figure 2. In vivo human cardiac hydrogen-1 (^1H) magnetic resonance spectroscopy. Spectrum consisting of 35 averages ($TR \geq 2800\text{ ms}$, $TE/TM = 10/7\text{ ms}$), from a 12.6 cm^3 voxel positioned in the interventricular septum of a healthy volunteer as shown in (B) and (C). Resonance assignment: (1) residual water, 4.7 ppm; (2) total creatine $-\text{CH}_2$, 3.9 ppm; (3) N-trimethyl groups, 3.2 ppm; (4) total creatine $-\text{CH}_3$, 3 ppm; (5) unsaturated fat, 2.0–2.3 ppm; (6) fat $(-\text{CH}_2)_n$, 1.3 ppm; (7) fat terminal methyl, 0.9 ppm. Spectrum acquired by Dr. Belen Rial, Oxford Centre for Clinical Magnetic Resonance Research.

Findings in DCM

Deranged cardiac energy metabolism is a hallmark of the failing heart [1], regardless of the etiology. In DCM, PCr to ATP ratios are reduced, correlating with the New York Heart Association (NYHA) functional class [4] and left ventricular ejection fraction [6]. Most importantly, they are a strong predictor of prognosis, and in one study the PCr to ATP ratio was a better predictor of long-term survival than NYHA class or left ventricular ejection fraction (*Figure 3*) [7]. Although PCr to ATP ratios are powerful indicators of the extent of energetic derangement in DCM, they still underestimate the true extent of metabolic derangement. Recent spectroscopy techniques have made the absolute quantification of ATP and PCr possible, showing approximately 50% reduction in PCr and 35% reduction in ATP, with a concomitant 25% decrease in the PCr to ATP ratio, in heart failure [8]. An even more sensitive indicator of deranged energetics may be the dynamic rate of turnover of ATP. Recently, ATP turnover (ATP flux through the creatine kinase reaction) was measured in volunteers and patients with heart failure; for an 18% reduction in PCr concentrations, a 50% reduction in the rate of turnover of ATP was demonstrated [9]. Thus, the measurement of ATP turnover rates holds promise as a highly sensitive indicator of energetic derangement in heart failure.

There are only two previous studies on ^1H -MRS in DCM. In a mixed group of patients with non-ischemic heart failure (15 patients, 11 of whom had DCM), Nakae et al. [10] found a nearly 50% decrease in total creatine content, which also correlated inversely with plasma brain natriuretic peptide (BNP) levels. Apart from an early proof-of-principle study [11], there are no data on ^1H -MRS-measured myocardial lipid levels in patients with DCM, and these studies are urgently needed.

Treatment studies

An important area is the use of MRS for monitoring energetic changes in the heart after novel forms of treatment of DCM. We showed that conventional treatment of DCM with beta blockers, ACE inhibitors and diuretics for 3 months significantly improved the PCr to ATP ratio, together with clinical improvement [12]. Most recently, a study of the use of the investigational drug trimetazidine in patients with heart failure of mixed etiology revealed that trimetazidine was associated with a 33% increase in the PCr to ATP ratio, concomitant with improvements in NYHA class and left ventricular ejection fraction (EF) [13]. In a recent study, we investigated the effects of chronic exercise on DCM, and found an improvement on EF after 8 months of therapy, achievable

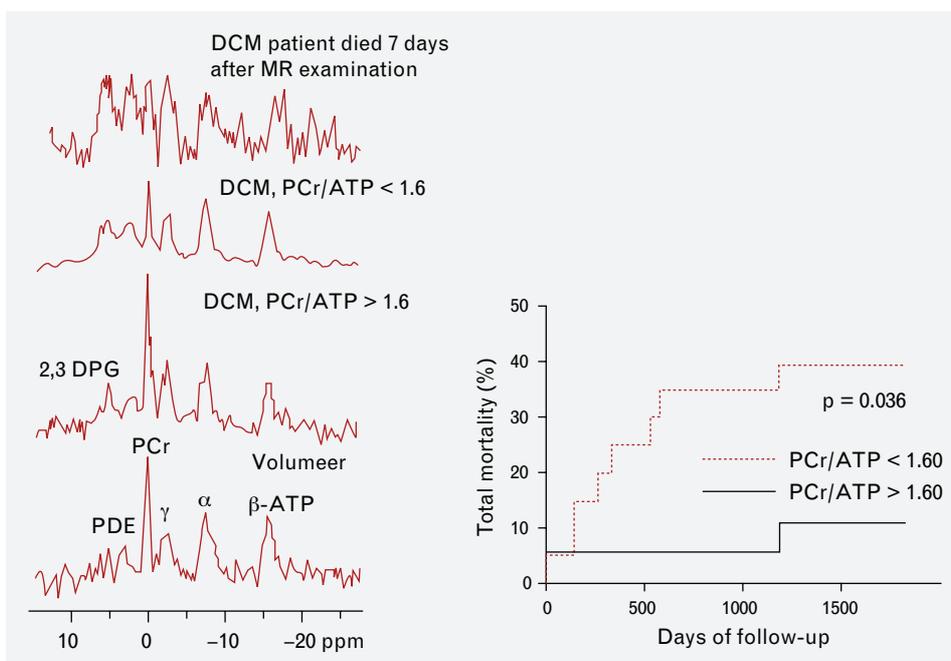


Figure 3. Phosphorus-31 (^{31}P) magnetic resonance spectroscopy in dilated cardiomyopathy. Left: ^{31}P magnetic resonance spectra in, from bottom upward: a healthy volunteer, a patient with mild dilated cardiomyopathy (DCM), a patient with severe DCM with reduced phosphocreatine (PCr) to adenosine-5'-triphosphate (ATP) ratio, and a patient who died 7 days after the magnetic resonance examination, showing a massive reduction in the PCr to ATP ratio. Right: Kaplan-Meier curve analysis of total mortality in DCM. Patients were subdivided according to the initial PCr to ATP ratio (greater or less than 1.60). Substantially increased mortality was observed in patients with an initially reduced PCr to ATP ratio. Modified from Beer M et al. [8]. ©2002 American College of Cardiology Foundation.

without extra energetic cost to the myocardium, as estimated by similar PCr to ATP ratios [14]. Although currently available studies on this subject are clearly limited by their small size, the concept of monitoring novel drug therapy for heart failure with regards to its effects on cardiac energetics is an extremely appealing one.

Future perspective

The main challenge for MRS is the improvement of the method's low signal to noise. Promising techniques on the horizon to achieve this are higher field strength (7T and more) and hyperpolarisation methods (for carbon-13 [¹³C] MRS) [15], which can boost the signal by several orders of magnitude, but require intravenous application of external hyperpolarized ¹³C metabolites. These are exciting novel directions for future research.

Summary

MRS allows for the non-invasive assessment of various aspects of cardiac metabolism in DCM, and has the potential to become an important biomarker tool for diagnostic and prognostic assessment as well as for the monitoring of therapy. ■

REFERENCES

1. Neubauer S. The failing heart—an engine out of fuel. *N Engl J Med*. 2007;356:1140–1151.
2. Bottomley PA. MR spectroscopy of the human heart: the status and the challenges. *Radiology*. 1994;191:593–612.
3. Hudsmith LE, Neubauer S. Magnetic resonance spectroscopy in myocardial disease. *JACC Cardiovasc Imaging*. 2009;2:87–96.
4. Clarke K, O'Connor AJ, Willis RJ. Temporal relation between energy metabolism and myocardial function during ischemia and reperfusion. *Am J Physiol*. 1987;253:H412–H421.
5. van der Meer RW, Doornbos J, Kozerke S, Schär M, Bax JJ, Hammer S, Smit JW, Romijn JA, Diamant M, Rijzewijk LJ, de Roos A, Lamb HJ. Metabolic imaging of myocardial triglyceride content: reproducibility of ¹H MR spectroscopy with respiratory navigator gating in volunteers. *Radiology*. 2007;245 (1):251–257.
6. Neubauer S, Horn M, Pabst T, et al. Contributions of ³¹P magnetic resonance spectroscopy to the understanding of dilated heart muscle disease. *Eur Heart J*. 1995;16 (Suppl O):115–118.
7. Neubauer S, Horn M, Cramer M, et al. Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. *Circulation*. 1997;96:2190–2196.
8. Beer M, Seyfarth T, Sandstede J, et al. Absolute concentrations of high-energy phosphate metabolites in normal, hypertrophied, and failing human myocardium measured noninvasively with P-SLOOP magnetic resonance spectroscopy. *J Am Coll Cardiol*. 2002;40:1267–1274.
9. Smith CS, Bottomley PA, Schulman SP, Gerstenblith G, Weiss RG. Altered creatine kinase adenosine triphosphate kinetics in failing hypertrophied human myocardium. *Circulation*. 2006;114:1151–1158.
10. Nakae I, Mitsunami K, Matsuo S, Matsumoto T, Morikawa S, Inubushi T, Koh T, Horie M. Assessment of myocardial creatine concentration in dysfunctional human heart by proton magnetic resonance spectroscopy. *MRM*. 2004;3:19–25.
11. Walecki J, Michalak MJ, Michalak E, Bilinska ZT, Ruzyllo W. Usefulness of ¹H MR spectroscopy in the evaluation of myocardial metabolism in patients with dilated idiopathic cardiomyopathy: pilot study. *Acad Radiol*. 2003;10 (10):1187–1192.
12. Neubauer S, Krahe T, Schindler R, et al. ³¹P magnetic resonance spectroscopy in dilated cardiomyopathy and coronary artery disease. Altered cardiac high-energy phosphate metabolism in heart failure. *Circulation*. 1992;86:1810–1818.
13. Fragasso G, Perseghin G, De Cobelli F, et al. Effects of metabolic modulation by trimetazidine on left ventricular function and phosphocreatine/adenosine triphosphate ratio in patients with heart failure. *Eur Heart J*. 2006;27:942–948.
14. Beer M, Wagner D, Myers J, Sandstede J, Köstler H, Hahn D, Neubauer S, Dubach P. Effects of exercise training on myocardial energy metabolism and ventricular function assessed by quantitative phosphorus-31 magnetic resonance spectroscopy and magnetic resonance imaging in dilated cardiomyopathy. *J Am Coll Cardiol*. 2008;51 (19):1883–1891.
15. Schroeder MA, Cochlin LE, Heather LC, Clarke K, Radda GK, Tyler DJ. In vivo assessment of pyruvate dehydrogenase flux in the heart using hyperpolarized carbon-13 magnetic resonance. *Proc Natl Acad Sci U S A*. 2008;105:12051–12056.
16. Neubauer, Stefan. Metabolic imaging with cardiac magnetic resonance spectroscopy. *Heart Metab*. 2009;44:17–20.