Magnetic Resonance Spectroscopy as a Clinical Tool for the Prognosis and Diagnosis of Diabetic Heart Disease

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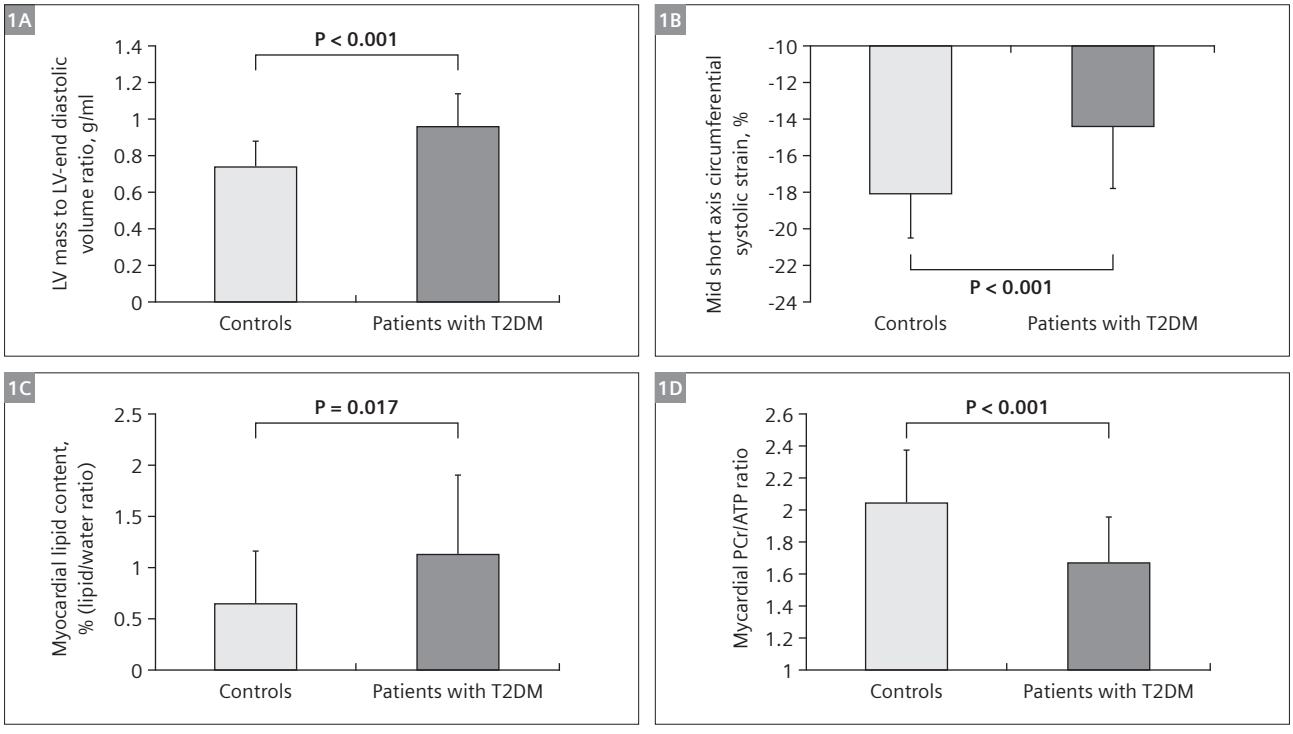
Introduction

Type 2 diabetes mellitus (T2DM) is often associated with an increased risk of heart failure and cardiovascular mortality. While the reasons for this are not fully elucidated, several possible mechanisms behind it have been proposed. These include impaired cardiac high energy phosphate metabolism, coronary microvascular dysfunction, and ectopic lipid deposition. Due to the complexity of these physiological phenomena, a combination of well-established diagnostic imaging methods, such as cardiovascular magnetic resonance imaging, ultrasound, computed and positron-emission tomography have so far been traditionally used for their investigation.

Although this combination of imaging techniques is extremely powerful, very few of these methods, if any, are able to provide insights into processes taking place at a molecular level – such as some dysfunctionalities in the cardiac energy metabolism (e.g. increased fatty acid usage, decreased lactate and glucose metabolization and/or high energy phosphate metabolization). This has led researchers and clinicians to examine the possibilities offered by magnetic resonance spectroscopy methods (particularly those based on interrogating ^{1}H and ^{31}P metabolites). Such complementary techniques add an additional layer of information to the results obtained via



1 Differences in cardiac geometry and function between patients with T2DM and control subjects: LV-mass-to-LV-end diastolic volume (EDV) ratio (grams/millilitre) **(1A)**, systolic strain (percentage) **(1B)**, myocardial triglyceride content (percentage) **(1C)**, and myocardial energetics (PCr-to-ATP ratio) **(1D)**. *Reproduced from [2] with the author's permission.*

clinical imaging protocols. As a consequence, during the last few decades, cardiac magnetic resonance spectroscopy has started to slowly become acknowledged as being a very formidable investigation tool, useful for both early detection and disease monitoring of diabetic heart disease.

Current applications of ^{1}H and ^{31}P cardiac magnetic resonance spectroscopy in the investigation of diabetic heart disease

Ectopic adiposity and cardiovascular disease prognosis
The number of type 2 diabetes mellitus patients is rapidly rising, and this increase is partially associated to the growth in obesity. A substantial amount of evidence demonstrates that excessive ectopic adiposity is common for patients with diabetes and it considerably increases the risk of cardiovascular disease, being very likely that it contributes to non-ischemic cardiomyopathy in this patient group.

^{1}H MRS has been successfully proven to be a very effective strategy for the quantification of myocardial triglycerides [1]. Later studies have demonstrated that type 2 diabetes is associated with an increase of ~ 31% of the LV-mass-to-LV-end diastolic volume (Fig. 1A) and almost two-fold increase in myocardial triglycerides (Fig. 1C, data acquired with a custom single voxel-based method), thus demonstrating that ^{1}H cardiac magnetic resonance data can be highly predictive of LV concentric remodelling and cardiac systolic strain [2].

From a practical perspective, ^{1}H magnetic resonance spectroscopy protocols for the assessment of cardiac steatosis are typically designed to quantify the amount of lipid deposition by measuring the ratio of the integral areas of the myocardial triglycerides' resonances and that of the water resonance respectively. Thus, they are designed as a two-step process, during which the myocardial triglycerides and the water are quantified independently in a small region of interest, usually located in the interventricular septum during mid-late diastole.

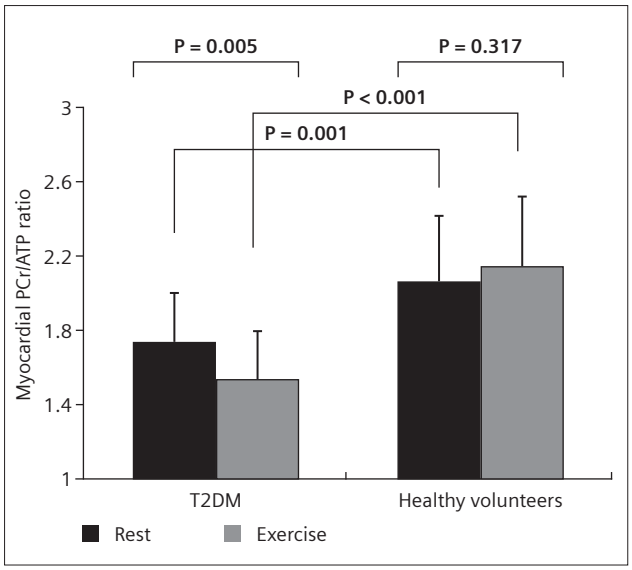
The most commonly employed acquisition strategies for ^{1}H cardiac spectroscopy are single voxel methods, which rely on either spin-echo [3] or stimulated-echo [4] excitation schemes. Spin-echo approaches have the advantage of higher signal to noise ratio compared to their stimulated-echo counterparts. The longer echo times imposed by the use of refocussing pulses for signal acquisition can lead to line broadening in the case of myocardial triglycerides, (which have an inherently long transverse relaxation rate) and subsequently, to difficulties in data quantification. Additionally, the use of spin-echo based methods, due to their higher sensitivity, can lead to the results being more susceptible to signal contamination, due to motion-induced involuntary detection of water in the blood pool surrounding the interventricular septum. Stimulated-echo methods are less sensitive to signal contamination and more suitable to the detection of myocardial triglycerides, as they allow for a shorter echo time to be employed. However, due to the fact that such strategies use gradients for signal refocussing, the signal decay during the echo time is governed by T2*, as opposed to T2 in spin-echo approaches, and dephasing due phenomena such as magnetic susceptibility and chemical shift difference.

For both methods, a careful choice of acquisition parameters is essential for accurate quantification: short echo times are highly recommended, and the repetition time needs to allow for full recovery of the two resonances (~ 2 s for myocardial triglycerides and ~ 4 s for water). The voxel is typically positioned parallel to the septum and its dimensions need to be adjusted in such a way that the volume of interest is large enough to warrant a reasonable SNR value, but not as large as to increase the risk of signal contamination due to the contribution of the surrounding blood pool during cardiac motion. To ensure data is always acquired at the same point in the cardiac cycle and to mitigate the effects of breathing artifacts, these examinations are typically performed using physiological triggers [5].

Measuring cardiac energy metabolism
The most energy-consuming reactions in the heart, such as the contraction of the myofilaments or the active pump function, are fuelled by the metabolization of adenosine triphosphate, which is obtained from phosphocreatine via the creatine-kinase process occurring in the mitochondria. Diabetic heart disease is associated with inefficient energy production or utilisation, which decreases the heart's ability to adapt when subjected to an increase in workload. Myocardial energy depletion can be caused by mitochondrial disfunction, poor energy transfer to the myofibrils and impaired uptake and use of adenosine triphosphate and phosphocreatine. Thus, the phosphocreatine-to-adenosine triphosphate ratio (PCr/ATP) is a very important biomarker which can be used to diagnose and monitor cardiac diabetic disease.

^{31}P magnetic resonance spectroscopy is the only non-invasive technique which can effectively quantify the PCr/ATP ratio. Changes in the cardiac energy metabolism, reflected in the PCr/ATP ratio, can take place before any subclinical or clinical manifestation of disease are reported or observed, we believe that ^{31}P magnetic resonance spectroscopy may become an invaluable tool for prognosis and diagnosis in the future.

Studies employing ^{31}P magnetic resonance spectroscopy have shown that the PCr/ATP ratio decreases considerably in the case of diabetic patients compared to healthy controls [6] and have demonstrated that diabetes is associ-

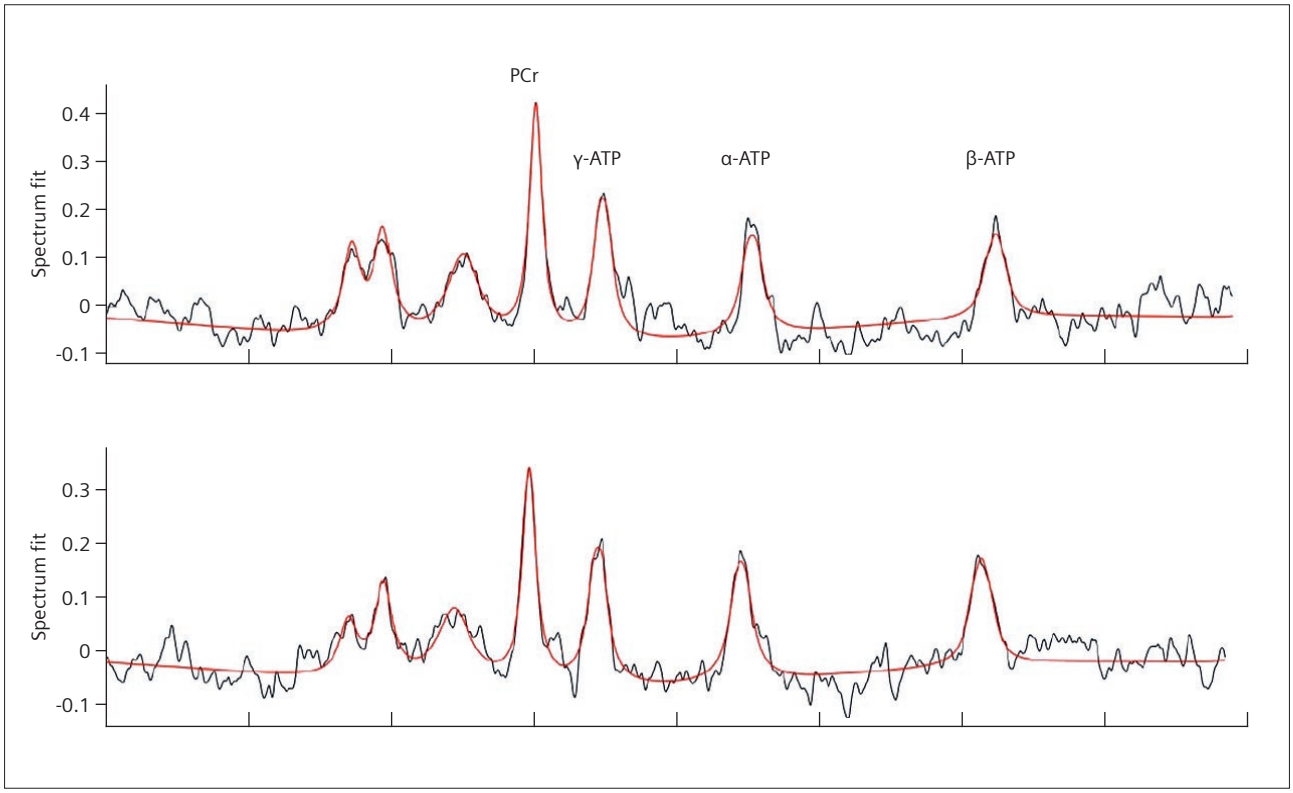


2 Differences in rest and exercise myocardial PCr/ATP ratios between controls and patients with T2DM. Bars show mean PCr/ATP ratios and error bars indicate standard deviations. *Reproduced from [7] with the author's permission.*

ated with a 17% decrease in PCr/ATP at rest compared with healthy volunteers, while a further 12% decrease was determined during exercise [7].

Our most recent research work at the University of Leeds is revolving around establishing the metabolic basis of heart disease in type 2 diabetes with a focus on exploring the role of metabolic inflexibility toward heart failure development and progression in type 2 diabetes, and the impact of diabetes on common cardiac comorbidities. We acquire ^{31}P spectroscopy data using a customised chemical shift imaging sequence, equipped with a spatially selective saturation module and a shaped excitation pulse tailored to effectively cover the full chemical shift range of interest [8]. The acquisition is ECG triggered and performed in free breathing (TR 720 ms, acquisition time ~ 9 minutes). Reproducibility is assessed by performing the same examination twice, while removing the patient from the scanner between the two consecutive scans.

Our results have confirmed the previous findings and have shown that a similar decrease in the PCr/ATP ratio is observed in type 2 diabetes patients while at rest and under stress, induced via dopamine infusion (Fig. 3).



3 ^{31}P spectra acquired in the interventricular septum and the corresponding fits. The spectra have been acquired on a type 2 diabetic patient at rest (top: PCr/ATP = 2.26 ± 8.0%) and during stress (bottom: PCr/ATP = 1.79 ± 8.4%).

Challenges and outlook

Both the effectiveness and the utility of magnetic resonance spectroscopy as a tool for cardiac disease prognosis and monitoring are generally recognised, but it has yet to become a routinely used method in the clinical environment. The most significant deterrents are the need for additional input from the examiner (when compared to standard cardiac magnetic resonance imaging methods), dedicated time for the pre-scan adjustments, such as B_0 shimming, the fact that ^{1}H methods are exceptionally sensitive to cardiac and respiratory motion and the need for dedicated hardware – broadband RF amplifiers and bespoke coils – in the case of ^{31}P.

However, given the fact that magnetic resonance spectroscopy can provide essential information prior to the development of clinical symptoms and considering the recent software developments for acquisition and processing, which have considerably contributed to making spectroscopy examinations easier for the routine user. We believe that magnetic resonance spectroscopy will soon claim its place among the methods used as a gold standard for measuring cardiac disease biomarkers, allowing for prognosis, early diagnosis and treatment planning.

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