High energy phosphate cardiac energetics are abnormal in Primary Biliary Cirrhosis patients in the absence of functional or anatomical abnormalities on structural MRI

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Introduction: Primary Biliary Cirrhosis (PBC) is an autoimmune liver disease affecting up to 20,000 patients in the UK, mostly affecting females from middle age. A follow-up study [1] of a geographically-defined cohort of 770 PBC patients found that their survival was much poorer than an age- and sex-matched population (standardised mortality ratio for PBC patients was 2.87). Excluding deaths from hepatic causes, the standardised mortality ratio for PBC patients was still 1.73: the balance of the risk was of a cardiac-related death but the mechanism by which the disease could affect cardiac tissue was unclear. ^{31}P MRS has been shown to be sensitive to changes in cardiac metabolism in advance of structural abnormalities [2], and in view of our previous work demonstrating mitochondrial abnormalities in exercising skeletal muscle [3], we speculated that signs of metabolic stress might be present in the phosphorus spectra of PBC patients as a precursor to cardiac damage, even if conventional structural parameters were found to be normal on imaging, as suggested from clinical experience of echocardiography.

Methods: 15 proven PBC Stage I-II patients (non-cirrhotic) were recruited and 8 age-, weight- and height- matched female subjects were recruited as controls. Phosphorus-31 magnetic resonance spectroscopy was used to measure cardiac high energy phosphate metabolism and high resolution imaging was used to assess cardiac morphology.

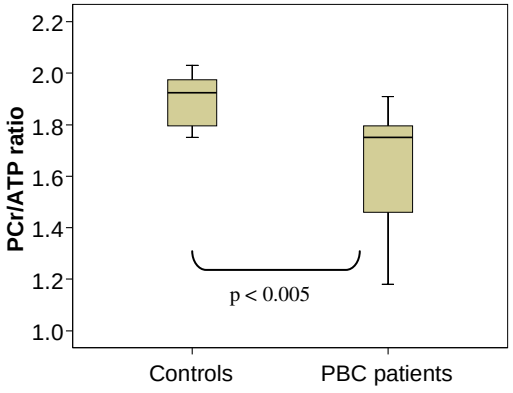

Figure 1 : PCr/γATP ratio for myocardial tissue in controls and PBC patients

MR protocol: (1) Spectroscopy Cardiac high-energy phosphate metabolism was measured using a 3T Intera Achieva scanner (Philips, Best, NL) with a 10cm diameter ^{31}P surface coil (Pulseteq, UK) for transmission/reception of signal and the in-built body coil for anatomical imaging. Subjects were placed in a prone position and moved into to the magnet so their heart was at magnet isocentre. Shimming was performed using a cardiac triggered, breath-held field map [4]. A slice-selective, cardiac gated 1-dimensional chemical shift imaging (1D-CSI) sequence was used with a 7cm slice selective pulse, with spatial pre-saturation of lateral skeletal muscle to avoid spectral contamination. 16 coronal phase-encoding steps were used, each 10mm thick (TR = heart rate, 96 averages, 20 mins). The first spectral line without skeletal muscle contamination was selected. Quantification of phosphocreatine (PCr), the γ resonance of adenosine triphosphate and 2,3-diphosphoglycerate (DPG) was performed using the AMARES time domain fit routine in the jMRUI processing software. After fitting the ATP peak area was corrected for blood contamination by 1/6 of the amplitude of the combined 2,3-DPG peak [5], and the PCr/ATP ratios were calculated and corrected for saturation, with T_1 values of cardiac phosphocreatine and ATP taken from the literature [6]. Flip angle correction was made using a gadolinium-doped 20mM phenyl phosphonic acid phantom at the centre of the coil [7,8].

(2) Cardiac morphology A dedicated 6-channel cardiac coil (Philips, Best, NL) was used for this acquisition with the subjects in a supine position and VCG gating. A stack of steady-state free precession images was obtained in the short axis view (TR/TE = 3.7/1.9ms, turbo factor 17, flip angle 40°, slice thickness 8mm, 0mm gap, 25 phases, temporal duration 50ms per phase), covering the entire left ventricle. Image analysis was performed using the cardiac analysis package of the ViewForum workstation (Philips, Best, NL). Manual tracing of the epicardial and endocardial borders was performed on the short axis slices at end-systole and end-diastole. Papillary muscles were included in calculations of mass and excluded from calculations of volume. The interventricular septum was included as part of the left ventricle. Left ventricular mass, ejection fraction, end-systolic and end-diastolic volumes were calculated. The body surface area was used to standardise the measurements for subject size (denoted in table 1 by the suffix "index") and this was estimated from the subjects' weight and height according to the formula of Dubois and Dubois [9]. Patient and control subject fatigue severity was assessed by means of a validated questionnaire, the Fatigue Impact Score (FIS), where 0 indicates no fatigue to a maximum of 160: this was done as ~50% of the PBC population suffer from profound fatigue, and the separate influences of the liver disease and fatigue must be tested [10].

Results: Figure 1 shows the PCr/γATP ratio for the controls and PBC patients. The PCr/ATP ratio is significantly lower for the PBC patients compared to controls (1.64 ± 0.23 vs 1.90 ± 0.10, $p < 0.005$, Mann-Whitney test). There are no significant differences between non-fatigued and fatigued patients, and no correlation between the PCr/ATP ratio and fatigue severity (FIS) or age in either group. Table 1 shows the morphological and functional parameters for the left ventricle. No significant differences are found in any left ventricular imaging parameters between the controls and PBC patients – there are no signs of any anatomical or functional abnormality. All the parameters estimated are within the normal range of females of this age group [11].

Table 1 : Subject characteristics and left ventricle morphology and functional parameters

	Controls	PBC patients
Age (yrs)	49.9 ± 8.7	52.3 ± 8.8
Weight (kg)	75.1 ± 10.9	67.9 ± 11.9
Height (m)	162 ± 6	161 ± 6
Body surface area (m^2)	1.80 ± 0.15	1.71 ± 0.15
Heart rate (bpm)	67.6 ± 10.9	69.1 ± 6.4
Cardiac output (l/min)	5.0 ± 0.5	4.8 ± 0.9
Ejection fraction (%)	65.6 ± 4.6	65.5 ± 3.5
LV EDV (ml)	118.4 ± 13.0	116.1 ± 21.1
LV ESV (ml)	40.6 ± 6.3	40.4 ± 9.8
Stroke volume (ml)	77.8 ± 11.0	75.7 ± 12.5
LV mass (g)	92.0 ± 6.9	90.6 ± 8.1
LV EDV index (ml/m^2)	67.2 ± 6.3	67.9 ± 9.4
LV ESV index (ml/m^2)	23.1 ± 3.7	23.7 ± 5.1
Stroke volume index (ml/m^2)	44.1 ± 5.3	44.3 ± 4.8
LV mass index (g/m^2)	52.2 ± 1.6	53.3 ± 4.0

EDV = end diastolic volume, ESV = end systolic volume.

Conclusion: We have successfully measured high energy phosphate levels in the hearts of primary biliary cirrhosis patients for the first time. It has been shown that there is a metabolic impairment compared to matched controls represented by a mean decrease of 14% in the phosphocreatine/ATP ratio. Our previous work in skeletal muscle leads us to speculate that this change may be mitochondrial in origin. Cardiac morphology from anatomical scanning, however, shows no significant impairment of ejection fraction, LV mass or stroke volume in PBC patients. It appears that a metabolic stress is present in PBC patients that is not explicable by structural disease. This study provides further evidence for primary biliary cirrhosis being a multi-system disease. The cardiac metabolic dysfunction detected here may increase the risk of future functional cardiac mortality: a longitudinal follow-up study will be required to confirm this.

Acknowledgements : MRC grant G0500020. Jessie Pairman, Katherine Wilton, Louise Morris, Carol Smith. **References:** [1] Prince M *Gastroenterol.* 2002;123:1044, [2] Lodi R *et al. Cardiovasc. Res.* 2001;52:111, [3] Hollingsworth *et al. Proc. ISMRM* 2008;16:612, [4] Schar *et al. Proc. ISMRM* 2002;10:1735, [5] Conway MA *et al. Circulation* 1998;97:1716 [6] Tyler *et al. Proc. ISMRM* 2006;14:3099, [7] Buchli *et al. MRM* 1993;30:552, [8] Haase A *et al. JMR* 1984;56:401, [9] Dubois *Arch. Intern. Med.* 1916; 17:863, [10] Jones DEJ *J. Hepatol.* 2003;39:639, [11] Hudsmith *et al. JCMR* 2005;7:5.