High energy phosphate metabolism in Primary Biliary Cirrhosis (PBC) patients monitored by ^{31}P magnetic resonance spectroscopy: abnormalities in pH handling

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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. Although, over many years, PBC can progress to end-stage liver disease and require liver transplantation, loss of quality of life for many is caused by profound, life-altering fatigue [1]. The mechanism of this fatigue is not understood and there are no effective treatments. 50% of PBC patients suffer from fatigue, irrespective of the severity of their underlying liver disease [2]. It is unclear whether this fatigue arises from central nervous system control or whether it has a peripheral component. As part of a larger study of both these mechanisms, phosphorus spectroscopy of the exercising calf muscle has been performed. Phosphorus spectroscopy is able to non-invasively probe the concentrations of high-energy phosphates (PCr, inorganic phosphate, ATP and pH) as a time course in exercising muscle, allowing us to measure patterns of metabolite consumption, renewal and pH handling in the muscle.

Methods: Patient and control fatigue was assessed by means of a validated questionnaire, the Fatigue Impact Score (FIS), where 0 indicates no fatigue to a maximum of 160. 15 proven PBC Stage I-II patients (non-cirrhotic) were recruited, 8 with low fatigue (FIS < 25) and 7 with severe fatigue (FIS > 70). 8 age-matched female subjects (FIS < 25) were recruited as controls, as well as a fatigue comparator group (FIS > 70) of 8 female chronic fatigue syndrome patients (with secondary causes for fatigue excluded). The subjects lay supine and were asked to perform plantar flexion (every 2s) against a fixed load within the bore of a 3T Philips Achieva MR scanner (Best, NL). Phosphorus spectra were collected (using a 14cm surface coil and 1D ISIS localization) from the gastrocnemius and soleus muscles (which enable plantar flexion) every 10 seconds for 3 minutes of rest, 3 minutes of exercise and a further 3 minutes of post-exercise recovery. Two exercise bouts were performed: (i) at 25% maximum voluntary contraction (MVC) to assess oxidative metabolism without changing tissue pH and (ii) at 35% MVC to cause greater anaerobic metabolism, lower pH and quantify efflux (removal) of protons from tissue during recovery from exercise. Data was fitted using a time-series model in MRUI and all exercise parameters were calculated using the methods in [3] using custom processing routines. All statistical comparisons were made using the Mann-Whitney U test.

Results: MVCs were equivalent between the subject groups and there were no significant differences in resting metabolite concentrations or pH.

(i) The 25% MVC exercise showed that PCr recovery following exercise was prolonged in the non-fatigued PBC patients compared to fatigued PBC patients, the latter group being identical to controls and CFS patients (fig 1). Half- time for ADP recovery was similarly prolonged (data not shown). Energetic recovery by oxidative phosphorylation is prolonged in non-fatigued patients.

(ii) Normal controls (fig 2a) and CFS controls (fig 2b) had a close correlation between the half-time for ADP recovery and the half time for PCr recovery, suggesting normal mitochondrial responsivity to exercise-generated ADP. This was not seen in either non-fatigued (fig 2c) or fatigued PBC patients (fig 2d).

(iii) Resting pH was the same in all three groups. In the 35% MVC exercise, PBC patients had a significantly greater pH drop (defined as resting pH minus minimum pH) with exercise than either normal or CFS controls (fig 3a). No difference in pH drop was seen between fatigued and non-fatigued PBC patients (data not shown). Across the PBC patient group as a whole a strong correlation was seen between PCr/ADP recovery half-time ratio and minimum pH value post-exercise (fig 3b).

(iv) The time taken for recovery of pH to the resting state value following cessation of exercise was also found to be abnormal in PBC patients, with prolonged recovery being seen in the majority of the study group (fig 4). Unlike pH drop, pH recovery time appeared to be related to fatigue severity in PBC, as those PBC patients with normal pH recovery (defined as pH recovery time < mean recovery time in normals + 2SD) had substantially lower fatigue severity (mean FIS = 19) than patients with prolonged pH recovery (mean FIS = 82).

(v) There is an increase in the time to maximum proton efflux from muscles in fatigued PBC patients (but not non-fatigued PBC patients) compared to controls (fig 5). Prolonged time to maximum proton efflux was also seen in the CFS control group indicating that, although in many respects CFS patients mimic normal controls, there are aspects of muscle pH handling which are abnormal in this important clinical group.

Fig 1

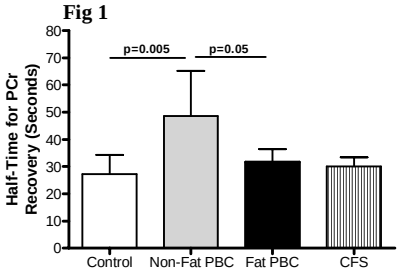


Fig 2a

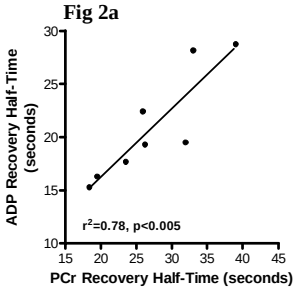


Fig 2b

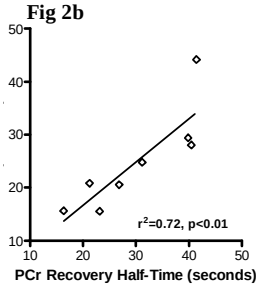


Fig 2c

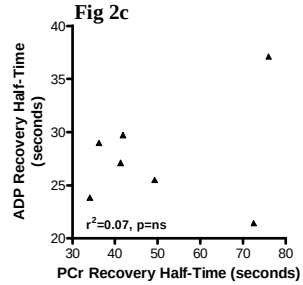


Fig 2d

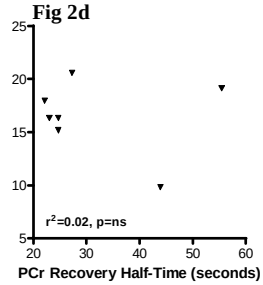


Fig 3a

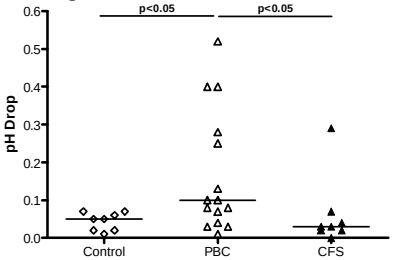


Fig 3b

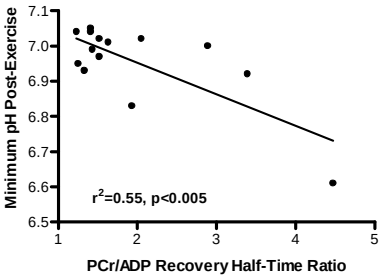


Fig 4

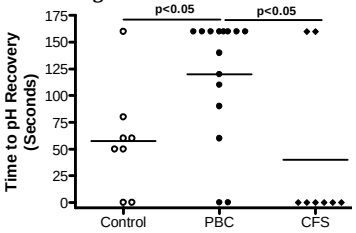
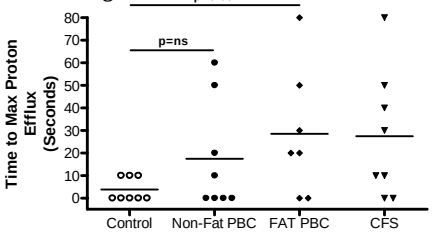


Fig 5



Conclusion: These novel observations indicate that PBC patients exhibit abnormality in intra-muscular pH regulation on exercise with rapid development of acidosis. This is followed by delayed recovery to baseline, with the time for pH recovery showing an association with perception of fatigue. The absence of this response in the CFS fatigue controls suggests it is not a deconditioning phenomenon. These results are in keeping with a model of fatigue sensation resulting from prolonged acidosis. The delayed time to maximum proton efflux in fatigued PBC patients may be due to known abnormalities in the sodium/proton anti-porter or vascular runoff due to autonomic dysfunction [4]. The PBC patients as a group show abnormalities in mitochondrial sensitivity. The prolonged half-time for PCr recovery in the non-fatigued PBC patients may assist these individuals by slowing the rate of proton production from this reaction. The results show pH handling abnormalities in both non-fatigued and fatigued PBC patients, and the differences in PCr recovery time may indicate a compensatory mechanism that is absent in fatigued patients. Further studies are being carried out to examine the origin of the delay in maximum proton efflux.

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