Cytosolic pH buffering in muscle of patients with McArdle's disease

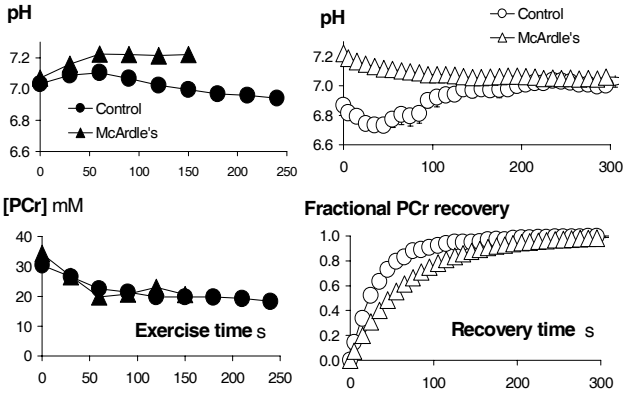
G. J. Kemp[1], C. Tonon[2], E. Malucelli[2], A. Liava[3], D. Manners[2], E. Trevisi[3], A. Martinuzzi[3], B. Barbiroli[2], and R. Lodi[2]

[1]Division of Metabolic & Cellular Medicine, University of Liverpool, Liverpool, Merseyside, United Kingdom, [2]Dipartimento di Medicina Clinica e Biotecnologia Applicata, Policlinico S. Orsola-Malpighi, Bologna, Italy, [3] "E. Medea" Scientific Institute, Conegliano Research Centre, Conegliano, Italy

Introduction. Cellular pH control is important in muscle cell physiology and metabolic regulation, and an understanding is essential for quantitative interpretation of ^{31}P MRS data from exercise and recovery (5). Cellular acidification results from coupled glycolytic ATP production and ATP hydrolysis, mitigated by cytosolic buffering and the effective 'consumption' of H^+ by regeneration of ATP at the expense of phosphocreatine (PCr). The concepts are still debated (3, 4, 7, 9) and data are limited (5, 8). Cytosolic buffer capacity (β) is not very well defined, because *ex vivo* methods are prone to artefact (1, 7), while MRS methods often make assumptions about ATP turnover and/or proton/lactate efflux (5) or need parallel direct lactate measurements (8). Study of very early exercise, when pH rises as a result of net PCr breakdown unopposed by lactate production, offers a simple approach (1, 2). However, it is difficult to acquire suitable data (if pH change in the first exercise point is negative or zero the method breaks down). McArdle's disease (myophosphorylase deficiency) offers the chance (6) to acquire several such data points, as pH does not decrease with exercise.

Methods. Ten McArdle patients (2 females, 34±10 y, mean±SD) with molecularly and biochemically characterized myophosphorylase deficiency and 12 controls (4 females, 33±10 y) were studied in a 1.5T GE Signa Horizon LX whole-body scanner. Subjects lay supine with a 6 cm surface coil centred on the maximum circumference of the right calf muscle. Spectra were acquired with TR= 5 s at rest (128 FIDs), during aerobic incremental plantar flexion exercise (10% lean body mass for 2 min, then increasing 5% LBM per minute) and recovery (64 FIDs, time resolution of 10 sec). Spectra were processed by the time-domain fitting routine AMARES/MRUI and the concentrations (mM i.e. mmol/l cell water) of inorganic phosphate (Pi) and phosphocreatine (PCr) were calculated, after saturation correction, by assuming a normal [ATP] of 8 (mM). pH was calculated from the chemical shift of Pi. Data are given as mean±SEM.

Results & Discussion. Fig 1 shows the time course and Fig 2 the analysis of buffering. Exercise data from patients are consistent (Fig 2) with simple buffering during consumption of H^+ by PCr breakdown (1, 2). The failure of recovery to retrace exactly the trajectory of exercise (Fig 2) suggests additional mechanisms, e.g. greater average buffering by bicarbonate in a more open system than exercising muscle, or small components of H^+ influx and/or efflux so far relatively unexplored in skeletal muscle at suprabasal pH.



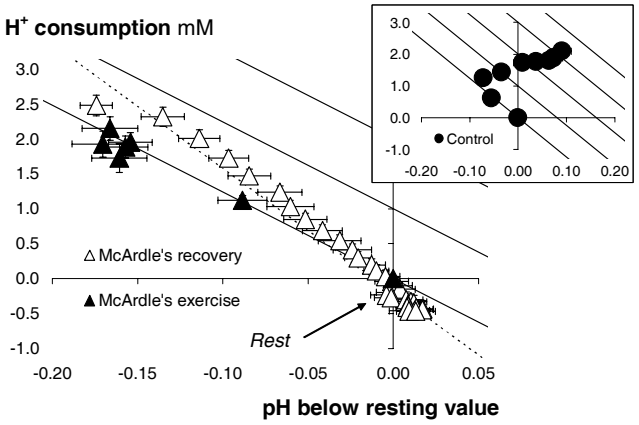


Fig 1. Time course of PCr and pH during exercise and recovery in McArdle's disease and controls (see key). Patients show reduced exercise duration with normal PCr fall while pH showed a marked rise instead of the normal rise and fall. Slow PCr recovery suggests mitochondrial impairment secondary to defective glycolytic pyruvate supply. Cytosolic [ADP] (not shown) was increased during exercise in patients and its recovery was slow.

Fig 2. Proton handling in patients with McArdle's disease (see key). Proton 'consumption' resulting from PCr fall is plotted against the fall in pH (in patients, negative during exercise = pH rise.). The exercise data lie on a straight line representing zero lactate production with buffer capacity β = 12±2 mM/(pH unit): the further lines to the right represent hypothetical lactate increments of 1 mM. Inset panel shows control exercise data for comparison: data points move rightward as lactate accumulates (reaching 6±1 mM), although the initial β is the same as in patients if lactate production is assumed negligible at this point. The recovery points (main panel) for patients shows PCr 'generation' by PCr resynthesis as pH returns to baseline appear to move on a different line (dotted), for which effective $\beta \approx 20$ mM/(pH unit), higher than in exercise.

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We acknowledge financial support by Telethon Italy (GUP03501)