# The pH-dependence of post-exercise PCr and ADP recovery: a simple modelling approach reproduces important features of 31P MRS data from skeletal muscle

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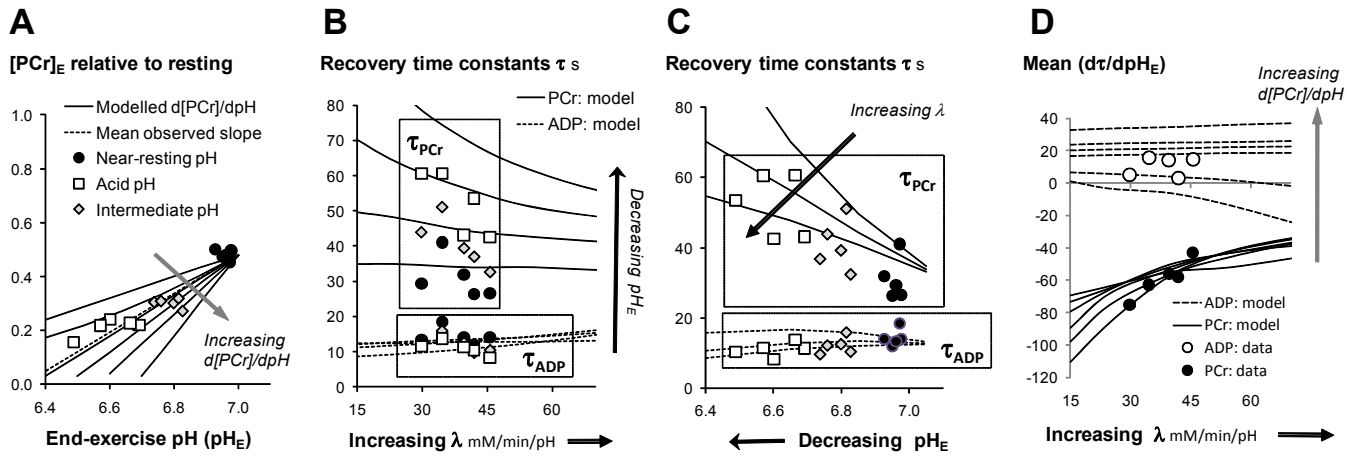
**Introduction.** Noninvasive $^{31}$P MRS measurements of the post-exercise recovery kinetics of pH, [PCr] and [ADP] contain much information about muscle mitochondrial function and cellular acid-base balance *in vivo*, but quantitative interpretation depends on understanding the physiology (*1-4*). Both analytical and simulation approaches may be useful, particularly given the interactions between these variables imposed by the creatine kinase equilibrium. The dependence of the phosphocreatine recovery time constant ($\tau_{PCr}$) on end-exercise pH ($pH_E$) is important in inferences about mitochondrial function, and the $pH_E$-dependence of the end-exercise/initial-recovery rate of acid efflux ($E_E$, which can be estimated from pH and PCr recovery data (*5*)) likely reflects a fundamental cellular physiological setting (e.g. higher in glycolytic fibres). It has recently been noted (*1*) that the slopes of these two relationships, $\lambda = -(dE_E/dpH_E)_{mean}$ and $(d\tau_{PCr}/dpH_E)_{mean}$, correlate across individuals, suggesting that intersubject differences in the pH-dependence of $\tau_{PCr}$ are related to differences in cellular pH control (*1*). It was noted (*1*) that a simple model reproduces the $pH_E$-dependence of $\tau_{PCr}$ (*2*). Here we show that, further, it directly predicts the $\lambda$-dependence of $(d\tau_{PCr}/dpH_E)_{mean}$ as well as individual values of $\tau_{PCr}$ and $\tau_{ADP}$, but that these depend also on the relationship between $pH_E$ and $[PCr]_E$, which is not under direct experimental control.

**Methods.** Experimental data and methods are as previously published (*1*). The basis of the model is that under the feedback influence (*3*) of [ADP] (which is in creatine kinase equilibrium with pH and [PCr]), oxidative ATP synthesis drives PCr recovery, this being accompanied by net $H^+$ generation (*4*) which is opposed by linearly pH-dependent $H^+$ efflux (*1, 5*). Values of mitochondrial capacity $Q_{MAX}$ and $\lambda$ are obtained from each subject's data, and assumptions about mitochondrial control and cellular buffering are described elsewhere (*4-8*).




**Results and Discussion**. Figure A shows relationships between $[PCr]_E$ and $pH_E$ in the present simulations (solid lines: $[PCr]_E$ is varied incrementally and $pH_E$ is obtained for various values of $d[PCr]_E/dpH_E$, increasing as the arrow indicates) and in the data points from each of the 5 subjects (*1*), sorted for clarity into means for each individual of studies where $pH_E$ was 'near-resting', 'intermediate', and 'acid' (a mean data $d[PCr]_E/dpH_E$ line is also shown: see legend for key). The more steeply $[PCr]_E$ decreases with $pH_E$, the more steeply $[ADP]_E$ increases (not shown).

Figure B shows simulated $\tau_{PCr}$ (solid lines) and $\tau_{ADP}$ (dashed lines) as a function of $\lambda$ for various values of $pH_E$, which here is varied holding $[ADP]_E$ constant: $\tau_{PCr}$ decreases markedly with increasing $\lambda$ while $\tau_{ADP}$ changes little. Figure C shows the same thing (with the same key) in a different way, the lines showing $\tau_{PCr}$ and $\tau_{ADP}$ as a function of $pH_E$ for various values of $\lambda$: the increase in $\tau_{PCr}$ with decreasing $pH_E$ is more marked at high efflux settings (high $\lambda$). The data points in Figures B & C (key as in Figure A) show that the experimental results (*1*) exhibit the same behaviour as the theoretical lines. The increase in $\tau_{PCr}/\tau_{ADP}$ as $pH_E$ decreases (Figure C) was recently reported in a patient group (*9*).

In Figures B & C $d[PCr]_E/dpH_E$ was chosen to keep $[ADP]_E$ constant as $pH_E$ is varied, but different assumptions are possible, and better match the experimental initial conditions in Figure A, where $[ADP]_E$ (not shown) rises modestly with decreasing $pH_E$. In the summary Figure D (which has a similar format to Fig 4B in the experimental paper (*1*)) each pair of lines (solid = $\tau_{PCr}$, dashed = $\tau_{ADP}$) makes a different assumption about $d[PCr]_E/dpH_E$ (as in Figure A). Figure D shows that the $pH_E$-dependence of $\tau_{PCr}$ decreases with increasing $\lambda$, while $\tau_{ADP}$ is insensitive to $\lambda$ except in the extreme case where $d[PCr]_E/dpH_E$ is so shallow that $[ADP]_E$ falls with decreasing $pH_E$.

Thus a simple model of mitochondrial control and acid efflux explains much of post-exercise PCr and ADP recovery in relation to $pH_E$. More generally, simple modelling can avoid some ambiguities of purely verbal argument about an multiply-interacting physiological system, and provide a bridge to more detailed mechanistic treatments of mitochondrial control (*8*) and acid handling by the myocyte.

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