Personalized Exercise Regimes to Generate OXPHOS Measurements using Integrated CrCEST and Carnosine Spectroscopy

Ryan R Armbruster[1], Dushyant Kumar[1], Blake Benyard[1], Paul Jacobs[1], Aditi Khandavilli[2], Liu Fang[3], Ravi Prakash Reddy Nanga[1], Neil Wilson[1], Shana McCormack[4], Anne Cappola[5], and Ravinder Reddy[1]

[1]Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA [2]Department of Nutrition and Science, Cornell University, Ithaca, NY, USA [3]Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA [4]Neuroendocrine Center, Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, PA, USA [5] Division of Endocrinology, Diabetes, and Metabolism, University of Pennsylvania, Philadelphia, PA, USA.

Introduction: CrCEST is sensitive to pH changes which can bias the creatine recovery time (τCr). To combat this issue, a method to measure pH pre- and post-exercise recovery and its impact on CrCEST MRI is clearly needed. In this study, we define a mild and moderate/intense exercise by using maximum voluntary contraction (MVC) and integrating ^{1}H-MR carnosine spectroscopy with 3D CrCEST.

Methods: 27 healthy subjects (14M; age range 21-42) were enrolled in an approved IRB protocol, and written informed consent was obtained. Two different types of plantar-flexion exercise, mild and moderate/intense, were performed in-magnet. 10 participants performed mild exercise and 17 participants performed both mild and moderate/intense exercise. All scans were performed on a 7T MRI scanner (MAGNETOM Terra, Siemens Healthcare, Erlangen, Germany) with a 28-channel phased-array knee coil (QED, Mayfield Village, USA). In each session, baseline and post-exercise acquisitions of CrCEST and carnosine spectroscopy were performed. The same parameters and calculation of CrCEST, WASSR, and B_1^+ map are the same as in our previous work.[4,5] No B_1^+ correction was performed; instead, placement of a dielectric pad on the LG helped to improve relative B_1^+ inhomogeneity.[6,7] The spectroscopy pulse sequence and optimal reference voltage calibration are the same as in previous work. [8,9] Spearman correlation coefficients were used to calculate the strength and direction of association between recovery rate and change in pH.

Results: Calf pH measurements at baseline, post-mild, and post-moderate/intense exercise are depicted in **Figure 1 A-B**. **Figures 2A-D** show CrCEST maps and recovery curves for mild and moderate/intense exercise. Across all participants, mild exercise had a median τCr of 62s[range:18-229s] and 51s[range:11-187s] in the LG and MG, respectively. Whereas moderate/intense exercise τCr in the LG and MG were 128s[range:53-750s] and 109s[39-548s], with a change in pH ranging from 0.1-0.7 units. For mild exercise, Spearman's correlation coefficient showed no significant correlation between recovery rate and change in pH; however for moderate/intense exercise a significant and strong correlation(ρ=0.67, p=0.001) was found between pH change and with τCr.

Discussion & Conclusion: Conventionally, pH shift and mild exercise have been measured and prescribed using ^{31}P-MRS and MVC, respectively. We show that carnosine spectroscopy paired with MVC can quickly and optimally prescribe a mild-exercise. Our findings indicate that the occurrence of intracellular acidosis results in delayed recovery of τCr with a significant and strong positive monotonic relationship. With the prescribed mild exercise stimulus, when a pH change of less than or equal to 0.1 units was achieved, the post-exercise CrCEST elevation was sufficiently high and the recovery time constant sufficiently long to be detected by our CrCEST MRI protocol, thus enabling measurement of OXPHOS.

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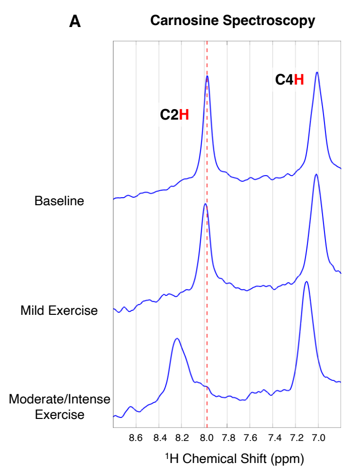

B

Induced pH shift

Exercise	PPM	pH
Baseline	7.98	7.06
Mild	8.00	7.03
Moderate/Intense	8.25	6.53

Fig. 1 (A) The C2 and C4 protons from the carnosine imidazole moiety resonate at ~8.0 and ~7.0 ppm, respectively. The red dotted line is drawn at the peak of the C2 proton to help visualize the ppm shift relative to each exercise. (B) The resultant ppm values are displayed with the calculated pH given by the adjusted Henderson-Hasselbach equation.

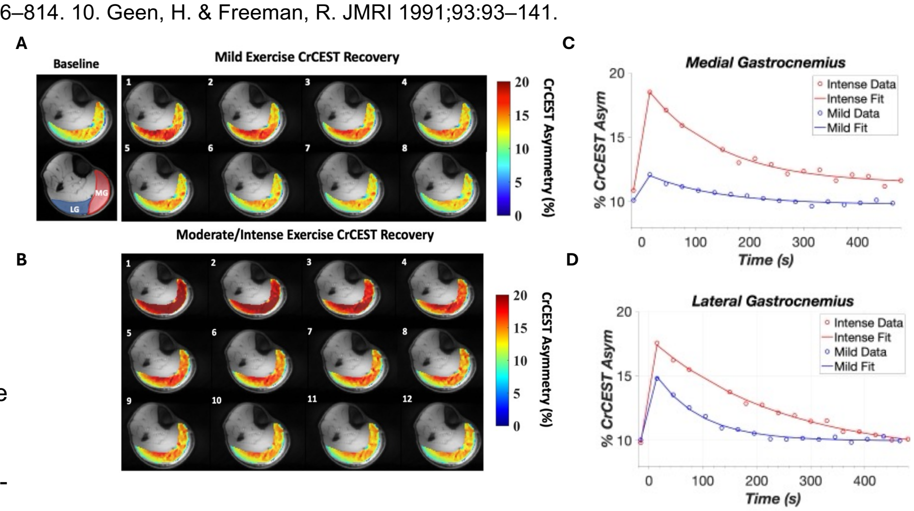

Fig 2. (A) Baseline CrCEST measurement and segmented gastrocnemius portions are displayed in red (MG) and blue (LG). The second panel of **A** displays CrCEST recovery maps captured at 30-second intervals. The same recovery diagram for intense exercise is displayed in **B**. CrCEST recovery curves are plotted for each muscle group in **C** and **D** which shows the post-exercise contrast enhancement and mono-exponential recovery.