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Cross-sectional Relationships Between Muscle ATP Synthesis, Ambulatory Performance, and Age: Initial Findings from the Baltimore Longitudinal Study on Aging (BLSA)

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Introduction: Although it is well-established that ambulatory performance, as defined by gait speed, is the single most reliable predictor of morbidity in the elderly [1], determination of key factors causing reduced mobility remains an open research question. Skeletal muscle mitochondrial function is thought to play a central role in mobility and consequently in the morbidity of the aging population [2]. ^{31}P MRS of skeletal muscle permits measurement of maximum ATP synthesis rate, an index of mitochondrial function, through the recovery time constant of phosphocreatine (τ_{PCr}) after exercise. In this cross-sectional study using data from the Baltimore Longitudinal Study of Aging (BLSA), we assessed the associations between muscle mitochondrial function, age and two ambulatory performance measures: usual gait speed (UGS) and rapid gait speed (RGS).

Methods: In vivo ^{31}P-MRS measurements of high-energy phosphorus-containing metabolites, inorganic phosphate, and pH were measured in the vastus lateralis muscle using a 3T Philips Achieva MR scanner (Philips, Best, The Netherlands) and a 10 cm ^{31}P-tuned surface coil (PulseTeq, Surrey, United Kingdom). All participants (n = 93, mean age 72±12 year, range = 43 - 92 year, male = 39, female = 54) were instructed to perform a quasi-static knee extension exercise protocol inside the magnet, consisting of strong and rapid quadriceps muscle contractions, following the protocol described by Jubrias et al. [3] ^{31}P MRS data were acquired at rest, during exercise, and during post-exercise recovery. The pulse sequence consisted of single adiabatic pulses of 90-degree flip angle applied with TR=1.5 s. Four scans were averaged for each time point, resulting in a 6 s interval between measurement time points, and 75 time points were acquired for a total acquisition time of 7.5 minutes. Acquired spectra were processed using jMRUI version 5.0 [4] and quantified using a nonlinear least squares algorithm (AMARES) [5]. Mitochondrial ATP synthesis was measured by fitting the time-course of PCr concentration during post-exercise recovery to a mono-exponential function: $PCr(t) = PCr(0) + \{PCr_{rest} - PCr(0)\}\{1 - \exp(-t/\tau_{PCr})\}$ using the R script language [6]. UGS and RGS were measured within three days of the ^{31}P-MRS measurements over a 6 m course in an uncarpeted corridor. Participants were instructed to walk at their normal pace for UGS and as quickly as possible for RGS. The faster of two trials performed for each walk were used for analysis. Pearson's product moment correlation was applied to evaluate the associations between τ_{PCr}, age, UGS, and RGS.

Results: τ_{PCr} showed a strong correlation with age (Fig. 1 and Table 1), with greater age being correlated with a longer bioenergetic recovery time constant. τ_{PCr} was correlated more strongly with RGS (Fig. 2, Table 1) than with UGS (Table 1). Both τ_{PCr} and RGS were more closely correlated with age than with UGS (Table 1). τ_{PCr} showed less variability over a similar range of age in men than in women (Fig. 3). RGS decreased more rapidly with age than UGS, as evidenced by a steeper negative slope in the regression analysis (Table 1).

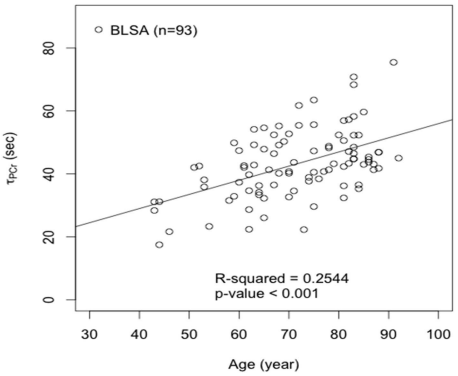

Fig. 1 τ_{PCr} (sec) vs. Age (year)

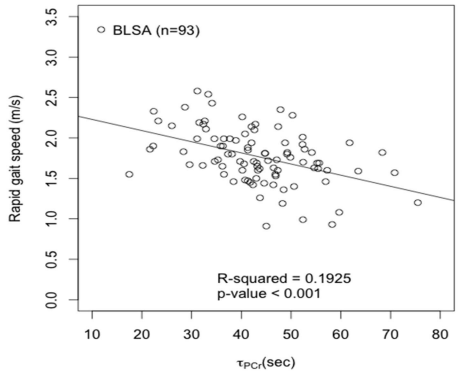

Fig. 2 Rapid Gait Speed (m/s) vs. τ_{PCr} (sec)

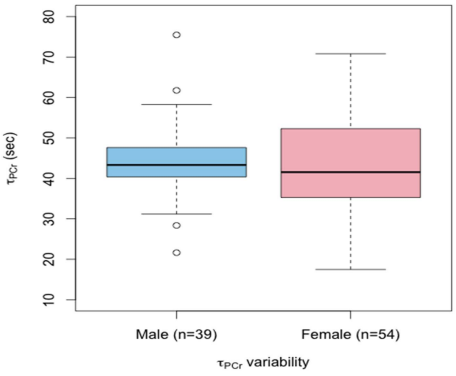

Fig. 3 Gender difference in τ_{PCr} variability

Discussion: These initial cross-sectional results from the BLSA show diminished mitochondrial function, as assessed from post-exercise ATP resynthesis, to be highly correlated with reduced ambulatory performance and advancing age. These results are consistent with work by Coen and colleagues from a smaller cohort (n=37) over a narrower age range (60-89 y). In that study, decreased mitochondrial synthetic capacity and whole-body aerobic capacity were associated with reduced ambulatory performance [2]. In our study, RGS was more strongly correlated with τ_{PCr} and age, which may imply that RGS is more limited by metabolic capacity than UGS. Thus, RGS may serve as a convenient assessment of ambulatory performance. Ongoing work in the BLSA cohort will permit the inclusion of other important physiological endpoints such as whole-body oxidative capacity, mitochondrial respiratory capacity (state 3 respiration), body composition, and ^{1}H MRS-derived muscle lipid content as well as 400 m gait speed. Most importantly, given the longitudinal and long-term design of the BLSA, the additional ^{31}P NMR measurements described here will ultimately provide a means of directly evaluating the influence of mitochondrial function on mobility and morbidity in the aging population.

Covariates	Correlations (r) Slopes (a)
τ_{PCr} vs. Age	r = 0.504, p < 0.001 a = 0.450, p < 0.001
UGS vs.τ_{PCr}	r = – 0.297, p < 0.005 a = – 0.006, p < 0.005
RGS vs.τ_{PCr}	r = – 0.439, p < 0.001 a = – 0.014, p < 0.001
UGS vs. Age	r = – 0.430, p < 0.001 a = – 0.008, p < 0.001
RGS vs. Age	r = – 0.533, p < 0.001 a = – 0.015, p < 0.001

Table 1 Correlations and slopes for τ_{PCr} versus functional variables

References: [1] Schrack et al. J Am Geriatr Soc 2010, 58: S329-S336, [2] Coen et al. J Gerontol A 2013, 68(4): 447–455, [3] Jubrias et al. J Physiol 2003, 533.2: 589-599, [4] Naressi et al. Comput Biol Med 2001, 31: 269-286, [5] Vanhamme et al. JMR 1997, 129: 35-43, [6] http://www.R-project.org.