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Mitochondrial Function in Physically Active Elders with Sarcopenia

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Abstract

Physical activity is reported to protect against sarcopenia and preserve mitochondrial function. Healthy normal lean (NL: n=15) and sarcopenic (SS: n=9) participants were recruited based on body composition (DXA, Lunar DPX™), age, and physical activity. Gastrocnemius mitochondrial function was assessed by ^{31}P MRS using steady-state exercise in a 4 T Bruker Biospin. Total work (429.3 ± 160.2 vs 851.0 ± 211.7 J, p<0.001) and muscle volume (p=0.006) were lower in SS, although these variables were not correlated (NL r=−0.31 p=0.33, SS r=−0.03, p=0.93). In the SS resting ATP/ADP was lower (p=0.03) and ATP hydrolysis higher (p=0.02) at rest. Free energy ATP hydrolysis was greater at the end of exercise (p=0.02) and [ADP] relative to total work output was higher in SS (ANCOVA p=0.005). [PCr] recovery kinetics were not different between the groups. Adjusting these parameters for differences in total work output and muscle volume did not explain these findings. These data suggest that aerobic metabolism in physically active older adults with sarcopenia is mildly impaired at rest and during modest levels of exercise where acidosis was avoided. Muscle energetics is coordinated at multiple cellular levels and further studies are needed to determine the loci/locus of energy instability in sarcopenia.

Keywords

Aging; Sarcopenia; Mitochondrial Function; Physical Activity

INTRODUCTION

The loss of skeletal muscle mass and alterations in contractile function known as sarcopenia is a common, though poorly understood phenomena of aging (Lee et al. 2007, Sowers et al. 2005). Although the origins of sarcopenia are yet unknown, oxidative stress and mitochondrial dysfunction are believed to play a role (Melov et al. 2007, Chabi et al. 2007, Semba et al. 2007). Recent evidence in sarcopenic gastrocnemius muscle of young and old rats revealed increased proteolysis, reactive oxygen species (ROS) overproduction and vulnerability to apoptosis (Martin et al. 2007). To further complicate this picture is the relationship between mitochondrial function and physical activity. Older adults may benefit from physical activity

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through the exercise-induced adaptation in cellular antioxidant defense and mitochondrial biogenesis (Ji 2001) and resistance training has been reported to "reverse" sarcopenia (Melov et al. 2007, Hunter et al. 2004, de Vos et al. 2005). However, strenuous exercise can increase muscle oxygen flux and elicit intracellular events that may lead to increased oxidative damage to mitchochondria (Ji 2001). Physical inactivity has also been linked to sarcopenia (Lee et al. 2007, Roubenoff 2000) and low intensity leisure-time physical activity alone appears inadequate in maintaining muscle mass (Raguso et al. 2006, Mitchell et al. 2003). Thus, the relationship between sarcopenia, mitochondrial function, and physical activity is reasonably complex. This investigation focused on comparing mitochondrial function in healthy community-dwelling older adults both with and without sarcopenia who reported long-term physical activity.

MATERIALS AND METHODS

Participants

Participants in the New Mexico Aging Process Study who previously expressed interest in participating in ancillary studies were contacted via letters to solicit interest in this study. Participants who met the age, body composition classification (normal lean or sarcopenic) and physical activity criteria were contacted. When recruitment for each age and body composition classification reached 50%, the groups were balanced for sex. Participants diagnosed with myopathies, severe peripheral arterial disease, or cancer cachexia, or who were taking corticosteroids, anabolic hormones, or other medications that might affect muscle mass and function were excluded. From this recruitment effort 15 normal lean and 9 sarcopenic participants were recruited. This study was approved by the University of New Mexico Health Sciences ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Body Composition

A Lunar DPX™ dual energy X-ray absorptiometer (DXA, Lunar Radiation Corp., Madison, WI) was used to measure total soft-tissue mass, % body fat, lean soft-tissue mass, and appendicular skeletal muscle mass. Percent coefficients of variation (%CV) were: 1.15% for total body fat mass, 0.51% for total body lean mass, 2.01% for lower extremity fat mass, 1.3% for lower extremity lean mass, 2.96% for upper extremity fat mass, and 1.96% for upper extremity lean mass.

Method for Defining Sarcopenia

At present, there is no agreement on the accepted criteria defining sarcopenia. We summed the appendicular skeletal muscle mass from DXA and divided by stature-squared (ASM/Ht^2) to provided an index of relative muscle mass. Using this criteria the participants were classified as normal lean (NL) with an ASM index ≥ 5.7 AND body fat $< 41\%$ for females, ASM index ≥ 7.6 AND body fat $< 30.6\%$ for males. Sarcopenic participants (SS) were classified by an ASM index ≤ 5.7 AND body fat $< 41\%$ for females, ASM index ≤ 7.6 AND body fat $< 30.6\%$ for males (Baumgartner 1998).

Magnetic resonance Image analysis was performed on a Cupertino, MacPro Macintosh computer (Cupertino, CA, USA.) using the public domain Medical Image Processing, Analysis and Visualisation program (MIPAV, developed at the U.S. National Institutes of Health and available on the Internet at http://mipav.cit.nih.gov/).

Physical Activity Assessment

Physical activity was assessed using an interview-administered validated questionnaire developed by Voorrips (Vorrips et al. 1991). The questionnaire includes frequency and duration of walking outside, bicycling, gardening, light household activities, heavy household activities, and sport activities during the preceding year. Household activities included questions that ranged from very active to inactive. Sports queried the type of activity and the number of hours per week and months per year spent doing specific activities. Scores were calculated using an intensity code based on net energy costs of the activities. The scores were summed to create a total physical activity score, for which there is no maximum by design. The questionnaire was administered by a trained research nutritionist and reviewed by an exercise physiologist. All participants reported life-long physical activity and their current levels of self-reported physical activity were compared to the previous 2 years to assure no large changes had taken place prior to the study.

Gait and Balance Functional Tests

To assess functional capacity, gait and balance measures collected on these participants in the same year of the annual NMAPS data collection was analyzed. Tinetti perfomance-based assessments (Tinetti et al., 1986) were administered by trained nurses and included 13 position changes: sitting balance; rising from a chair, immediate and prolonged standing balance; balance with eyes closed; turning balance; withstanding a nudge on the sternum; neck turning, back extension; reaching up; bending over to pick-up an object; and standing on one leg without support for five seconds. Gait speed had two trials where the number of steps and time to walk twelve feet was recorded. The first trial was at a normal pace. The second trial was as fast as possible for the participant.

^{31}P MRS methodology

All ^{31}P MRS experiments were conducted 4 hours after a standardized meal and greater than 24 hours following any exercise. The participants reported to the Aging and Genetic Epidemiology Unit the day prior to the ^{31}P MRS study to obtain consent, DXA scan, and a bagged breakfast to eat the following morning at 7:00. The next morning they reported to the University of New Mexico General Clinical Research Center (GCRC) and were transported to the MIND institute for ^{31}P MRS testing. Studies were conducted on a 4 T Bruker Biospin system (Billerica, MA). Participants lay supine in the bore of the magnet with a dual tuned proton/phosphorus (^{1}H/^{31}P, Nova Medical Wilmington, MA) transmit/receive coil secured around the gastrocnemius and the foot was secured into the exercise apparatus as previously described (Waters et al. 03). Each subject completed three trials to achieve an approximated one maximal voluntary contraction (1MVC). Housing of the magnet did not allow for a true 1MVC to be obtained. Participants performed a steady-state exercise protocol at 20% of the 1MVC for 8 minutes. Total work was determined by a force transducer interfaced to a computer running Data Translation Measure Foundry" Software (Data Translation, Inc., Marlboro, MA). Readings were acquired by the encoder at rate of 8 readings per second.

The location of the gastrocnemius within the magnet was confirmed by T_1 weighted ^{1}H localizing images obtained in the axial plane. An anatomical scan allowed the placement of the cross sectional image slab to be acquired using a 3D T_1 weighted gradient refocused echo sequence (fov = 200 × 200 mm, matrix = 256 × 256, 96 slices, with a 1 mm slice thickness) giving a final resolution of 0.8 mm × 0.8 mm × 1.0 mm. Shimming on the proton signal from tissue water was used to optimize the magnetic field homogeneity. Chemical shift imaging (CSI) ^{31}PMRS data was then acquired at 68 MHz with a one-pulse, phase-encoding spectroscopy sequence from a 40-mm thick axial slice that included the gastrocnemius muscle. The field of view was 20 cm × 20 cm and the matrix size was 8 × 8, producing a nominal voxel size of 25 cm^3. The repetition time was 2 s, resulting in a total acquisition time of 128 s per

CSI image or time point. Participants were asked to rest for the first four CSI acquisitions and then to press on the pedal to raise the weights at the rate of 34 repetitions per minute for 8 CSI acquisitions. The contraction rate was maintained by the audible switching on and off of the scanner's magnetic field gradients set at a 2-s recycle time. After 8 minutes participants were instructed to rest for 10 minutes.

Quantification of mitochondrial function and muscle energetics

Data were downloaded via Ethernet to a workstation for analysis using jMRUI software (Naressi et al. 2001). For visualization, each FID was processed with a 5 Hz exponential line broadening before zero filling and Fourier transformation. All spectra were manually phased using zero and first-order phase corrections. Resonance peak areas for phosphocreatine (PCr), inorganic phosphate (Pi) and adenosine tri-phosphate (ATP) were measured by time-domain curve-fitting using AMARES (Vanhamme et al. 1997) in jMRUI. Baseline cytosolic [PCr], [Pi], and adenosine diphosphate concentration ([ADP]) were calculated as previously described (Waters et al. 2003, Kemp et al. 2007). Intracellular pH was determined from the chemical shift (δ) of Pi relative to PCr as previously described (Kemp et al. 2007). Time constants (τ) during recovery, were calculated using non-linear regression. Data were then averaged across the four voxels contained within the gastrocnemius muscle. To compute variability among the voxels that were averaged, we used a coefficient of variation (CV, 100*standard deviation/mean) computed for each subject at each time and these are summarized for reporting by medians. Across all subjects and times, the median CVs were 3% PCr, 12% Pi, 12% ADP, and 8%ΔGp.

The molar free energy of cytosolic ATP hydrolysis was calculated according to $\Delta G_p = \Delta G_p^\circ + RT \log_e([ADP][Pi]/[ATP])$, where concentrations are expressed as Molar units and R=0.00831 kJ/(mol*K) and T=310 Kelvin and ΔG_p° is assumed equal to −32.8 kJ/mole at 37° C (Jeneson et al. 2000).

Statistical Analysis

All data are reported as means ± S.D. Non-parametric Wilcoxon tests were conduced on the anthropometric characteristics, total work, ΔG_p and [PCr], [Pi], [ADP] pH at rest and end of exercise. The relationship between variables was determined from linear regression analysis and Pearson correlation coefficient. Normalization procedures for total work (Mattei et al. 2002), and muscle volume and area with of the ^{31}P MRS variables were utilized. Statistical analyses were conducted using SAS software (SAS, version 9.1 Cary, NC) and a significance was accessed by $p<0.05$ for all tests.

RESULTS

Participants

Table 1 demonstrates no differences in age or height between the groups. Weight and ASM differed by group as per study design. Total activity score was not significantly different between the groups.

Self-reported physical activity

The primary physical activities were light gardening (n=4 SS, n=9 NL), heavy gardening (n=5 SS, n=6 NL), and fast walking/hiking (n=3 SS, n=4 NL). Ten participants reported a home exercise routine (n=4 SS, n=6 NL) and 2 people reported engaging in resistance training (n=2 SS). Total physical activity score which included household and leisure activity was 251 ± 79 and 280 ± 167 for the NL verses the SS, respectively. There was no significant difference between the groups for total physical activity score although the standard deviation was larger

in the sarcopenic group due to one participant reporting very high levels of physical activity. The comparison of activity scores between groups was not affected by the outlier in the sarcopenic group (either by t-test with Satterwaithe's correction for unequal SD, or nonparametric Wilcoxon test) so it is unlikely that it affected our results.

Gait and Balance Functional Tests

There were no statistically significant differences between the NL and SS for any of the gait and balance functional tests.

Mitochondrial Function and Muscle Energetics: ^{31}P MRS

Rest—At baseline (rest) [Pi] was marginally, but significantly greater (p=0.02), ATP/[ADP] lower (p=0.03), and ATP free energy hydrolysis (ΔGp) higher (p=0.02) in the SS compared to NL (Table 2).

Exercise—ATP normalized to [PCr] (ATP/PCr) was lower during exercise in the SS compared to the NL (p=0.03). [ADP] relative to total work output was significantly greater in the SS (p= 0.005 ANCOVA, Figure 1). The free energy released by ATP hydrolysis (ΔG_p) was greater (i.e. less negative) at the end of exercise in the SS compared to the NL. The rates of ATP hydrolysis (slope) did not differ, but the intercept was significantly lower in the SS compared to the NL (p=0.02, Fig 2).

Recovery—There were no differences between the groups in recovery kinetics for any of the metabolic parameters studied.

Muscle Volume and Total Work

Although the groups had been matched for physical activity and performed identical 1MVC tests, the total work performed during exercise was significantly less in the SS group (429.3 ± 160.2 vs 851.8 ± 211.7 J, p< 0.001). Our study design used appendicular skeletal muscle (ASM) mass cut-scores to classify participants as normal lean or sarcopenic. Thus, it was anticipated that the gastrocnemius muscle volumes would be lower in SS than for normal lean participants by study design. Magnetic resonance Image analysis was performed on a Cupertino, MacPro Macintosh computer (Cupertino, CA, USA.) using the public domain Medical Image Processing, Analysis and Visualisation program (MIPAV, developed at the U.S. National Institutes of Health and available on the Internet at http://mipav.cit.nih.gov/). This revealed both muscle volume and cross sectional area were lower in the SS (both p=0.006, Table 2). However, total work and muscle volume were not correlated either for the NL (r=−0.31 p=0.33) or SS (r=−0.03, p=0.93), or for pooled data (r+0.30, p=0.19). Correlations for NL and SS were not different (interaction (not shown), p=0.58).

DISCUSSION

Summary of findings

To our knowledge, this is the first study to investigate mitochondrial function in healthy older adults that are both physically active and sarcopenic. The sarcopenic group performed significantly less total work during exercise and had significantly less muscle volume compared to normal lean counterparts. However, these variables were not correlated. In the sarcopenic participants, ATP/ADP was lower and ATP hydrolysis higher at rest. ATP/PCR was lower during exercise, ATP hydrolysis was greater at the end of exercise, and [ADP] relative to total work output was higher in the sarcopenic participants. The rate at which mitochondria resynthesized [PCr] during recovery were not different between the groups. Adjusting for differences in total work and muscle volume did not change these findings.

Mitochondrial Function and Muscle Energetics

Mitochondrial oxidative ADP phosphorylation is the primary source of ATP in skeletal muscle during aerobic exercise (Wu et al. 2007). In healthy people the control of oxidative phosphorylation by substrate concentrations (Pi and ADP) allows the mitochondria to maintain free energy of ATP hydrolysis over a range of work loads (Wu et al. 2007). Thus, changes in the concentrations of ADP and Pi generated by utilization of ATP in the cell, affects the rate at which mitochondria utilize those products to resynthesize ATP (Beard D.A., 2005). Our investigation did not reveal a greater drop in ΔG_p at the rest-work transition in the sarcopenic group or were there differences between the groups during exercise. There was a difference in the relationship of ΔG_p to total work at the end of exercise, and slightly greater free energy utilization during rest and recovery periods in the sarcopenic participants. Abnormalities in ΔG_p at rest and in response to work have been reported in patients with complex I deficiencies (Wu et al. 2007). Patients with chronic heart failure also have anormalities in ΔG_p in concert with elevated [Pi] at rest and high [ADP] response to lower power outputs, This result agrees with our findings and a retrospective analysis of our data confirmed that our sarcopenic participants did not have diagnosed chronic heart failure. Lower ATP turnover during exercise (e.g. lower ATP/PCR) in the sarcopenics could indicate they were altering their work output to preserve metabolic homeostasis. Kemp et al. (Kemp et al. 2001) proposed that the most affected muscles generate less force, with a consequently smaller [ATP] turnover that, in effect, is the muscle's inherent ability to protect itself against metabolic perturbations. Although we can not verify this, it could explain the unexpected low total work output by the sarcopenics.

Overall, these data suggest aerobic metabolism in gastrocnemius muscle of physically active sarcopenic adults is mildly impaired at low intensity steady-state exercise under conditions where acidosis was avoided. However the level of defect is difficult to resolve. Actomyosin ATPase, Ca^{2+} ATPase in the sarcoplasmic reticulum, and mitochondrial ATPase are all involved with maintaining ATP free energy in skeletal muscle (Jeneson et al., 2000). Moreover, skeletal muscle mitochondria function is coordinated at multiple cellular levels, which include transcription of two genomes, protein and lipid synthesis, and the assembly of protein complexes into a functional respiratory chain. Thus, dysfunction at any step could lead to the decreased ATP production that would negatively impact energy homeostasis (Hood et al. 2006). Differences in muscle characteristics, in addition to cellular mechanisms, need to be considered.

Muscle Volume and Function

Muscle volume and cross sectional area (CSA) were lower in sarcopenic participants, which was expected due to our study design using cut- scores that would differentiate the groups based on ASM. Decreased CSA and intrinsic force has been previously reported in sarcopenia (Thom et al. 2007). We reported no relationship between total work and cross sectional area or muscle volume, which agrees with Thom et al (Thom et al. 2007) who normalized the torque-velocity relationship to CSA and found it only explained 10% of the difference between younger and older men. Accordingly, when we adjusted data for differences in total work (Mattie et al., 2002), and for muscle volume it did not contribute to explaining the differences between the sarcopenics and normal lean groups (data not shown). If as discussed above, the sarcopenic participants were not unconsciously decreasing work output to preserve metabolic homeostasis, muscle loss may result in a decreased torque in dynamic (rather than static contraction) due to both the loss of sarcomeres in parallel and in series (Leiber and Friden 2000). Other factors such as deterioration of muscle quality, reduced muscle agonist muscle activation, or increased antagonist muscle coactivation could also play a role (Thom et al. 2007).

Isometric contractions are commonly used in ^{31}PMRS studies in order to significantly deplete [PCr] and decrease pH. In the current and a previous study (Waters 2003), we employed a protocol that used steady-state short contractions to obtain the desired signal-to-noise ratio and to maintain pH near normal (Slade et al. 2006). The exercise intensity and percent drop in [PCr] in this investigation was similar to our earlier study of active and inactive younger and older adults (Waters et al. 2003). Kemp et al (Kemp et al. 2001) also employed lower percentage MVC in order to achieve small pH changes and reported that this simplifies the analysis of PCr recovery (Kemp et al. 1999). A future investigation utilizing isometric contractions may provide additional insights into muscle energetic and mitochondrial function in sarcopenia.

Physical Activity and Mitochondrial Function

In this study we demonstrated that oxidative phosphorylation capacity during recovery from exercise was similar between the normal lean and sarcopenic participants while energy production during rest and exercise was compromised in the sarcopenic participants. A novel feature of this study was identifying both normal lean and sarcopenic people with similar levels of long-term physical activity. Several studies have reported no age-related mitochondrial dysfunction when levels of physical activity are controlled (Brierley et al. 1997, Kent-Braun & Ny 2000). Conversely, Conley (Conley et al. 2000) reported that mitochondrial dysfunction accounted for >50% of the loss of mitochondrial capacity in older adults with a reduction in mitochondrial content accounting for the remainder. Reduced mitochondrial content has been related to physical inactivity (Irrcher et al. 2003) and we attempted to control for this by selecting physically active sarcopenic adults. Although, self-report of physical activity has inherent problems of bias through non-differential misclassification, the participants were accustomed to reporting physical activity in the main longitudinal study and the objective measures of physical function support the evidence that the groups were not functionally different.

Aerobic exercise has been linked to increased electron transport chain activity (Menshikova et al. 06), mitochondrial biogenesis (Irrcher et al. 03) and reduced oxidative damage. Most of these improvements are achieved through moderate intensity exercise rather than strenuous activities which increase ROS production (Ji 01). Conditioning skeletal muscle through aerobic exercise significantly shortens the transition time of recovery kinetics (Phillips et al. 1995), accelerates oxygen-uptake kinetics at the onset of exercise, and improves ATP/ADP stability during work (Korzeniewski and Zoladz 03). These improvements come primarily from increased mitochondrial protein content and increase in the direct stimulation of oxidative phosphorylation complexes accompanying stimulation of ATP consumption during exercise (Korzeniewski 03). Thus, the lack of difference during recovery from exercise may be a training effect whereas the differences during rest and exercise could be related other components of skeletal muscle energy regulation such as differences in neural input, actomyosin ATPase or Ca^{2+} ATPase activity in the sarcoplasmic reticulum. It is also possible that our sampling time of two minutes per energetic measure was not short enough to detect a difference in recovery rate. Resistance training has been reported to “reverse” sarcopenia (Melov et al. 2007, Hunter et al. 2004, de Vos et al. 2005) and although resistance training positively impacts muscle myofibril volume, it does not change the mitochondrial compartment (Hoppeler et al. 03).

Conclusions

These data suggest that aerobic metabolism in physically active older adults with sarcopenia is mildly impaired at rest and during modest levels of exercise where acidosis was avoided. Muscle energetics is coordinated at multiple cellular levels and further studies are needed to determine the loci/locus of energy instability in sarcopenia.

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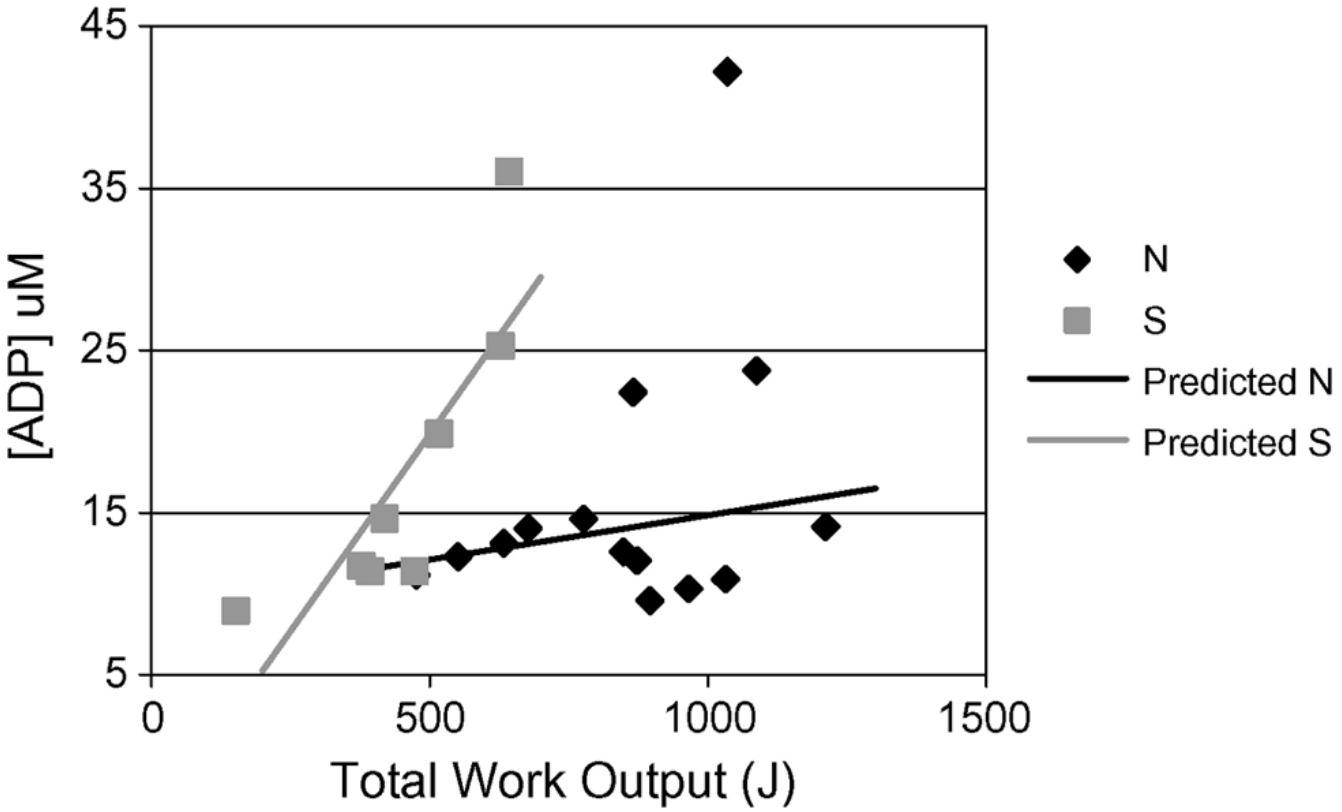

Figure 1.
Relationship of [ADP] to total work output at the end of exercise. N= normal lean, S= sarcopenic. p=0.005 ANCOVA difference in slope interaction

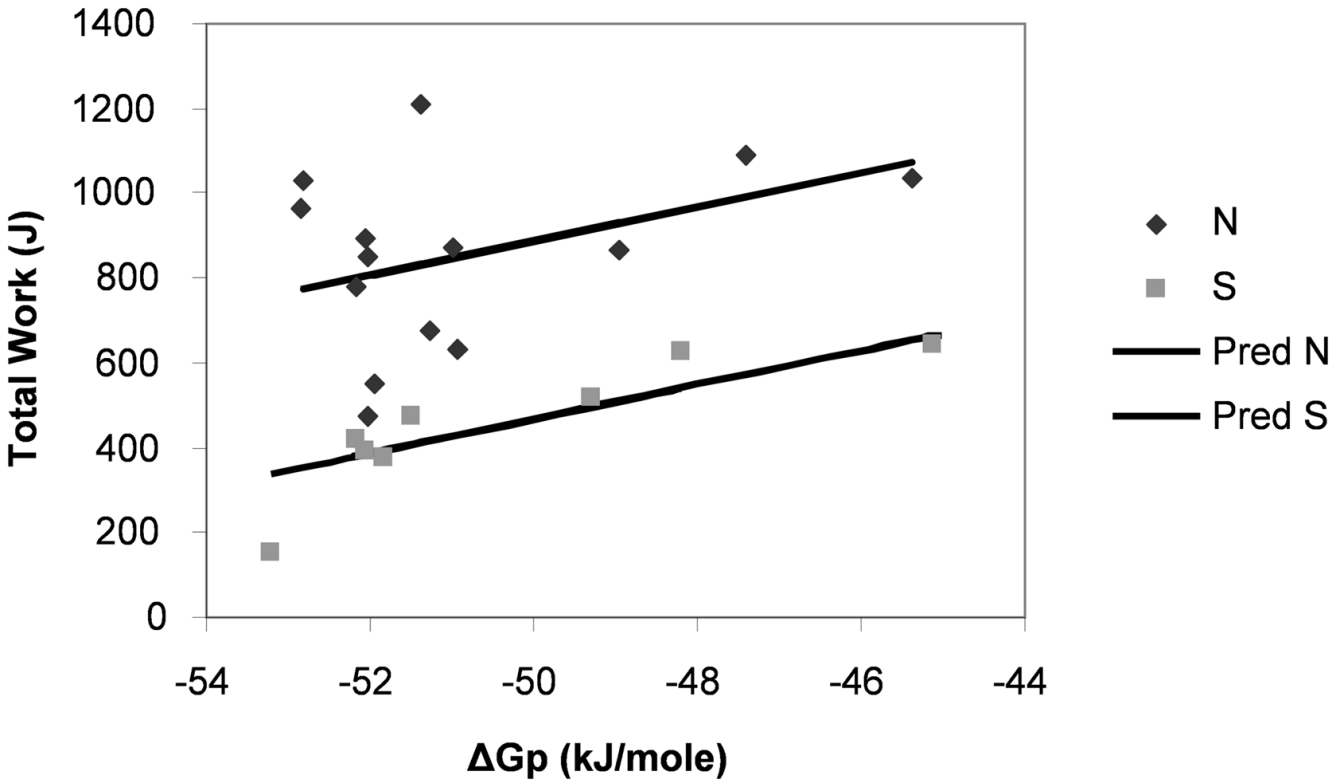

Figure 2.
Relationship between free energy ATP hydrolysis (ΔGp) and total work at the end of exercise. No difference in the slope between N (normal lean) and S (sarcopenic). Intercept significantly lower in S compared to N (p=0.02).

Table 1

Characteristics of Subjects

Characteristics	Normal Lean (N=15)	Sarcopenic (N=9)
Age (yr)	78.0 ± 4.9	79.3 ± 5.2
Height (cm)	165.0 ± 8.7	166.8 ± 7.5
Weight (kg)	70.3 ± 11.4	62.2 ± 14.1*
ASM index	6.7 ± 0.9	5.8 ± 0.9*
Muscle Volume (cm^3)	408.8 ± 66.9	327.8 ± 52.7*
Muscle cross- sectional area (cm^2)	10.2 ± 1.7	8.2 ± 1.3*
Activity Score	251.0 ± 79.0	280.0 ± 167.0

Values are shown as means ± SD. ASM index = appendicular skeletal muscle mass index/height^2 (ASM/m^2). Activity score is in arbitrary units.

* Significant difference between Normal lean and Sarcopenic groups, $p<0.05$.

Table 2

^{31}P MRS data at baseline and end of exercise.

^{31}P MRS Variables	Normal Lean (N=15)	Sarcopenic (N=9)	P-Value
[PCr]mM Rest	35.5 ± 1.8	36.4 ± 3.6	0.35
[Pi] mM Rest	3.4 ± 0.5	3.8 ± 0.4	0.02*
pH Rest	6.99 ± 0.01	6.99 ± 0.02	0.98
[ADP] μM Rest	4.7 ± 0.6	5.3 ± 0.8	0.10
[PCr]/[Pi] Rest	10.6 ± 1.5	9.5 ± 1.3	
ATP/[PCr] Rest	0.0036 ± 0.0003	0.0035±0.0006	0.42
ATP/[ADP] Rest	0.0266 ± 0.0038	0.0234 ± 0.0028	0.03*
ΔGp Rest (kJ/mole)	−56.2 ± 0.6	−55.7 ± 0.5	0.02*
[PCr] mM End of Exercise	28.9 ± 3.8	28.7 ± 4.4	0.94
[Pi] mM End of Exercise	9.9 ± 6.7	9.8 ± 6.1	0.91
pH End of Exercise	7.03 ± 0.03	7.02 ± 0.06	0.62
[ADP] μM End of Exercise	15.9 ± 8.6	17.4 ± 9.3	0.72
ΔGp End of Exercise (kJ/mole)	−52.12 ± 2.16	−52.68 ± 2.70	0.06†
PCr t1/2 (seconds)	43.8 ± 21.4	57.2 ± 36.9	0.19

Values are shown as means ± SD.

*Significant difference between normal lean and sarcopenic group,

†for trend in significance between normal lean and sarcopenic group ($p<0.05$).