Skeletal muscle mitochondrial function and lean body mass in healthy exercising elderly

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Abstract

Background: The decline in muscle mass (sarcopenia) with aging may be related to a decline in mitochondrial function. However, investigators have yet to reach a consensus as to whether a decline in mitochondrial function can be attenuated by physical activity has yet to reach a consensus.

Methods: Using dynamic 31PMRS to measure mitochondrial function, we measured baseline Phosphocreatine (PCr), inorganic phosphate (Pi), phosphodiester (PDE), [ADP], pH and recovery times (t1/2) for PCr and [ADP] following exercise, in 45 older (73 ± 4 years, SD), and 20 younger subjects (25 ±4 years, SD) who were matched for body mass across high and low activity levels and within age and sex groupings.

Results: Baseline PCr, and Pi, were lower, and PDE higher in the older subjects compared to younger subjects (all P < 0.01). The t1/2ADP was longer in older subjects (P < 0.001) controlling for age and sex in the low activity group (P = 0.02). In the older low activity groups, t1/2PCr was longer than high activity groups. Higher PDE levels were positively correlated with longer t1/2PCr in the older low activity females (both P < 0.05).

Conclusions: Our data suggests that mitochondrial function declines with age in healthy, exercising elderly adults and that the decline appears to be influenced by the level of physical activity.

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Keywords: Aging; Exercise; Mitochondria

1. Introduction

Whereas losses in lean body mass with aging (sarcopenia) is well described (Baumgartner et al., 1992, 1995; Evans, 1995; Navarro et al., 2001), a scientific opinion about a decline in mitochondrial function in healthy exercising elderly adults has not reached a consensus (Brierty et al., 1997b; Conley et al., 2000; Jubrias et al., 2001).

The loss of muscle mass with aging is characterized by progressive structural and functional changes in muscle. These changes are likely to be multi-factorial and symptomatic of reductions of motor neuron units, other changes in the nervous system, altered contractility and enzyme activity levels, poor nutrition and/or disease, reduced blood flow and cardiac output, and decreased physical activity (Vandervoort, 2002). It has been proposed that cumulative damage to skeletal muscle mitochondrial DNA (mtDNA) during aging reaches a threshold above which the accumulated damage begins to affect mitochondrial function, and ultimately results in cell death and the loss of muscle mass (LBM) (Bua et al., 2002; Cortopassi and Wang, 1995; Lenaz et al., 1997; Wanagat et al., 2001).

Physical exercise increases oxidative stress on skeletal muscle, but appears to have a positive effect on mitochondrial density and function (Brierty et al.,...
activity levels that matched the older volunteers. The 20 younger subjects were also divided into four groups: males and females, and high or low levels of activity and matched between high or low levels of physical activity for lean body mass, within sex grouping. The University of New Mexico Human Research Review Committee (IRB) approved the protocol, and written informed consent was obtained from all subjects.

2.2. Body composition

A Lunar DPX™ dual energy X-ray absorptiometer (Lunar Radiation Corp., Madison, WI) was used to measure percentage body fat, and total lean body mass for all subjects. Appendicular skeletal muscle mass and an appendicular skeletal muscle mass index were determined. Because muscle mass is correlated strongly with skeletal size, an index of sarcopenia that expresses muscle mass adjusted for variation in stature, or ‘relative muscle mass’ was used (Baumgartner et al., 1998). This approach is similar to that used for expressing ‘relative weight’ and defining levels of ‘overweight’ and ‘obesity’ from body mass index. When appendicular skeletal muscle mass is divided by stature-squared (ASM/S²) an index of relative muscle mass is generated that minimizes the correlation of muscle mass with stature across and between sex and age groups.

2.3. Physical activity assessment

Physical activity was assessed in all subjects using a modified, interview-administered questionnaire developed and validated by Voorrips et al. (1991). This questionnaire queried specific household and exercise activities over the past year. It was administered by a trained research nutritionist and reviewed by an exercise physiologist. Information was gathered regarding how much time was spent in low, moderate and high-intensity activities for the preceding year. Household and exercise scores were summed to achieve a total activity score and were used to classify subjects into low or high categories of activity. The subjects reported consistent levels of physical activity for at least 3 years prior to the study.

It is important to note that the activity scores in both the younger and older low activity categories reflected that these individuals were not sedentary. Rather, they engaged in some form of low intensity exercise (primarily walking) on an average of 2–3 times a week for approximately 20 min per exercise session. In terms of metabolic equivalents (MET) with one MET being equivalent to 3.5 ml kg min⁻¹ of oxygen, low activity exercise such as walking on a level solid surface at speeds from 53.7 to 80.5 m min⁻¹ (2–3 miles per hour), would produce an energy expenditure of 2.5–2.9 METS (8.8–11.5 ml kg min⁻¹). The high active groups engaged...
in 40–60 min of intense aerobic exercise 5–7 days per week. Thus, jogging or running on a solid surface outdoors at 0% grade at 134–188 m min⁻¹ (5–7 miles per hour), would result in an energy expenditure of 8.6–11.7 METS (30.1–40.95 ml kg min⁻¹). Some individuals in the high activity groups also performed resistance training, but they were matched for lean body mass with individuals in the low activity group to control differences in lean body mass.

2.4. Muscle mitochondrial function—dynamic 31P MRS

All MRS experiments were conducted > 6 h after the last meal and > 24 h after any exercise. Experiments were performed at 1.5 Tesla (General Electric Medical System, Waukesha, WI). Subjects lay supine in the bore of the magnet with a 31P transmit/receive flex coil centered on the lower leg at the level of the gastrocnemius and the foot secured into the exercise apparatus. The location of the gastrocnemius within the magnet was confirmed by T1 weighted 1H localizing images obtained in the axial plane. The sensitive volume of the coil limited the volume of the tissue sampled in the superior–inferior direction along the leg. The region of interest was selected from multislice, transaxial flex-coil proton images of the subject’s calf acquired at the center, proximal and distal ends of the coil. Even in the subject with the smallest medial gastrocnemius the signal contamination from non-selected regions should have been < 5% as previously reported (Walter et al., 1997).

Magnetic field homogeneity was optimized by shimming on the proton signal from tissue water. 31P MRS data were then acquired at 25 MHz from a 60 mm coronal slice, which included the gastrocnemius muscle. The exercise apparatus was a rigid frame with a wheel and a line connected the outer radius on one side of the wheel, over a pulley to a hook suspending calibrated weights from a frame. The weight to be lifted was calculated for each subject using 15% of the total lean body mass obtained from DEXA as described previously (Kemp et al., 1993). Regression analysis of appendicular skeletal mass (ASM) from DEXA confirmed that 15% of total lean body mass was highly correlated to ASM (P < 0.001, r² = 0.81). Contraction of the gastrocnemius allowed for a 9 cm vertical displacement of the weights.

Free induction decays (FIDs) of 1024 complex points were sampled using a spectral width of 2000 Hz, and a recycle time of approximately 2 s. Four FIDs were averaged and successively written to disk (every 8 s) during 64 s of rest, 12 min of exercise, and 10 min of recovery. Thus, a total of 92, 8 s averages were acquired continuously over 23 min. Each subject performed five repetitions prior to data collection for familiarization of the movement. Contraction rate was 30 repetitions per minute with standardization maintained by controlling contraction frequency using the audible gradient noise of the scanner acquisition set at a 2 s recycle time.

Data were downloaded via Ethernet to a workstation for analysis using MRUI software (MRUI, European Community) in the time domain. For visualization, each FID was processed with 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 PCr, ATP, and Pi were measured by line fitting of the spectrum using MRUI software. Signal-to-noise ratios were sufficient to allow PCr, Pi and ATP to be quantified with a temporal resolution of 8 s during exercise and recovery.

Baseline (rest) cytosolic [PCR] and [Pi] were calculated from the signal intensity ratios PCr/ATP and Pi/βATP respectively, taking ATP at rest to be 8.2 mmol l⁻¹ cell water (Kemp and Radda, 1994; Kemp et al., 1993) as follows:

\[ [\text{PCR}] = (\text{PCr}/\beta\text{ATP}) \times 8.2 \text{ mmol l}^{-1} \]

Metabolite peak areas were normalized to 100% by using the average metabolite value obtained during the 1-min rest (pre-exercise) as a reference. Concentrations were expressed as the percent change from baseline levels. Thus, PCr and Pi, indicate peak areas obtained from spectra and [PCR] and [Pi] are calculated concentrations.

To improve the signal to noise ratio, data points representing mean values at rest, end of exercise, and end of recovery were calculated by averaging two consecutive spectral collection points.

Cytosolic [ADP] was calculated as follows:

\[ [\text{ADP}] = ([\text{TCr}]/[\text{PCR}] - 1)[\text{ATP}]/(K/[\text{H}^+] \times 25) \]

where [TCr] = total creatine = 42.5 mmol l⁻¹ cell water, and K is the equilibrium constant of creatine phosphokinase (1.66 × 10⁹ l mol⁻¹) (Kemp and Radda, 1994; Kemp et al., 1993). Relative changes of PCr, Pi, and [ADP] were expressed graphically as percentages of the resting average as previously described (Yoshida and Watari, 1993).

Intracellular pH was determined from the chemical shift (δ) of Pi relative to PCr using the equation:

\[ \text{pH} = 6.75 + \log_{10}[(\delta - 3.27)/(5.69 - \delta)] \]

Time constants (t₁₂) for [PCr] and [ADP] utilization during recovery, were calculated using non-linear regression. The following model equation was suitable for the metabolic parameters:

\[ y(t) = S + (C₀ - S)\exp(-kt - 736), \]

where y(t) was the level of the metabolic parameter at the time (t) measured in seconds, C₀ was the level at the
Table 1
Subject demographics

<table>
<thead>
<tr>
<th>Age/sex group</th>
<th>Activity group</th>
<th>Age (year)</th>
<th>Lean body mass (kg)</th>
<th>Appendicular skeletal muscle mass index</th>
<th>Appendicular skeletal muscle mass</th>
<th>Activity score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Older</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females (n = 13)</td>
<td>High</td>
<td>73.8 ± 4*</td>
<td>39.5 ± 3.9*</td>
<td>16.3 ± 2.1*</td>
<td>6.4 ± 0.8*</td>
<td>22.3 ± 5.3*</td>
</tr>
<tr>
<td>Females (n = 10)</td>
<td>Low</td>
<td>73.2 ± 3*</td>
<td>36.8 ± 3.4*</td>
<td>14.3 ± 1.4*</td>
<td>5.9 ± 0.5*</td>
<td>14.1 ± 5.2</td>
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<td>Males (n = 10)</td>
<td>High</td>
<td>73.6 ± 5*</td>
<td>57.6 ± 4.0*</td>
<td>25.2 ± 2.5*</td>
<td>8.2 ± 1.0*</td>
<td>28.9 ± 8.1*</td>
</tr>
<tr>
<td>Males (n = 12)</td>
<td>Low</td>
<td>74.3 ± 6*</td>
<td>58.5 ± 5.8*</td>
<td>24.2 ± 2.9*</td>
<td>7.9 ± 0.9*</td>
<td>17.7 ± 6.4</td>
</tr>
<tr>
<td><strong>Younger</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females (n = 5)</td>
<td>High</td>
<td>26.4 ± 4</td>
<td>43.2 ± 3.6†</td>
<td>18.7 ± 1.9</td>
<td>6.6 ± 0.4</td>
<td>26.4 ± 3.6†</td>
</tr>
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<td>Females (n = 5)</td>
<td>Low</td>
<td>25.8 ± 4</td>
<td>41.8 ± 3.3†</td>
<td>18.3 ± 1.7</td>
<td>7.1 ± 0.1</td>
<td>15.5 ± 4.6</td>
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<td>Males (n = 5)</td>
<td>High</td>
<td>26.4 ± 2</td>
<td>60.0 ± 2.0</td>
<td>26.2 ± 3.5</td>
<td>8.9 ± 1.1</td>
<td>30.6 ± 6.3†</td>
</tr>
<tr>
<td>Males (n = 5)</td>
<td>Low</td>
<td>23.4 ± 3</td>
<td>61.3 ± 5.5</td>
<td>27.7 ± 3.4</td>
<td>8.8 ± 1.1</td>
<td>15.6 ± 7.2</td>
</tr>
</tbody>
</table>

Data reported as means ± SD.
* P ≤ 0.05 for age group differences (older > younger) differences.
† P ≤ 0.05 for sex group differences (males > females).
‡ P ≤ 0.05 for activity group differences (low < high). Differences expected by the study design.

beginning of recovery defined to be at 736 s, and \( k \) was the rate constant in units \( s^{-1} \). The time to 50% full recovery was related to the rate constant \( (k) \) by the formula:

\[
t_{1/2} = \ln 2/k.
\]

Box plots were used to show the relative distribution of Phosphodiester resonance area peaks between younger and older subjects.

2.5. Statistical analyses

Descriptive data (age, lean body mass, appendicular skeletal muscle mass, appendicular skeletal muscle mass index, and activity scores) were analyzed using Student’s \( t \)-test and reported as mean ± SD. Baseline concentrations for PDE, [PCr], and [Pi], calculated [ADP], pH, and time constants, were analyzed using three-way analysis of variance with age, activity, and sex as the grouping factors. Age, activity, and sex interactions are also reported if significant. These variables are reported as mean ± SE. For all analyses, differences were considered significant when \( P \leq 0.05 \).

3. Results

3.1. Demographics (Table 1)

Overall, males had greater lean body mass than female subjects (\( P < 0.05 \)) and the older group had significantly less lean body mass, appendicular skeletal muscle mass and appendicular skeletal muscle mass index than the younger group (\( P < 0.01 \)). As designed, there was no difference in the total lean body mass, appendicular skeletal muscle mass, or appendicular skeletal muscle mass index between activity levels within each of the age and sex groupings (Table 1).

3.2. \( ^{31}P \) MRS-baseline concentrations (Table 2)

3.2.1. Age-related differences

Baseline [PCr] and [Pi] were significantly lower in older subjects (each \( P < 0.001 \), Table 2). PDE resonance peaks were significantly greater in older subjects than in younger subject (\( P < 0.0001 \), Fig. 1). There were no differences in [ADP] or pH (\( P = 0.61 \) and 0.59, respectively).

3.2.2. Activity-related differences

[ADP] and [Pi] were significantly lower in the low activity groups (\( P < 0.001 \) and \( < 0.01 \), respectively).

3.3. \( ^{31}P \) MRS—relative changes normalized to baseline during exercise (% change)

3.3.1. Age-related differences

Minimum [PCr] was significantly lower (Fig. 2A and B), and maximum [ADP] were significantly higher (Fig. 3A and B) in the older group compared to the younger group (\( P = 0.01 \) and 0.02, respectively).

3.4. [ADP], and [PCr] time constants \((t_{1/2})\) during recovery

3.4.1. \( t_{1/2}^{ADP} \)

Overall, \( t_{1/2}^{ADP} \) was significantly longer in the older group controlling for sex and activity (\( P = 0.02 \), Table 3,
In the younger groups, there were no significant differences in $t_{ADP}^{1/2}$ due to sex or activity, whereas in the older group, $t_{ADP}^{1/2}$ was significantly longer in the low activity group for both males and females ($P < 0.05$).

Fig. 4). In the younger groups, there were no significant differences in $t_{ADP}^{1/2}$ due to sex or activity, whereas in the older group, $t_{ADP}^{1/2}$ was significantly longer in the low activity group for both males and females ($P < 0.05$).

3.4.2. $t_{PCr}^{1/2}$

A sex × age interaction was present for $t_{PCr}^{1/2}$ ($P = 0.02$) due to longer $t_{PCr}^{1/2}$ in the older, low activity females and younger, high activity males (see Section 4). In the elderly females, $t_{PCr}^{1/2}$ was significantly correlated with PDE ($r = 0.55$, $P = 0.03$)

4. Discussion

The goal of this study was to establish if mitochondrial function is lower in healthy, non-sarcopenic exercising elderly adults compared to younger exercising adults. It is important to note that the elderly subjects in this study had significantly lower levels of lean body mass, and appendicular skeletal muscle mass, but were matched between high and low levels of physical activity within age and sex groupings. By focusing our study on low and high levels of physical activity in healthy, non-smoking subjects matched for lean body mass across activity groupings, we made an effort to control for differences in lean body mass due to exercise, and to exclude subjects who might have peripheral vascular disease.

We chose a sub-maximal, steady state exercise for numerous reasons including that all participants could perform it, pH remained constant, it provided greater specificity to oxidative ATP synthesis, reduced the influence of fatigue mechanisms, and is physiologically relevant to the aging population. Although higher intensity exercise could have been used, other investigators have shown that recovery from steady-state oxidative exercise is a sensitive non-invasive measurement of mitochondrial capacity (Kemp and Radda, 1994; Kemp et al., 1993; McCully et al., 1993).

We also included the measure of [ADP] because it is considered to be a sensitive index of mitochondrial function and is best applied when interpreting steady-state (aerobic) exercise and recovery such as was employed in our study (Kemp and Radda, 1994; Kemp et al., 1993). [ADP] reflects mitochondrial ATP production and when mitochondrial function is im-

Table 2
Baseline [PCr], [Pi], pH, [ADP]

<table>
<thead>
<tr>
<th>Age group</th>
<th>Sex group</th>
<th>Activity group</th>
<th>[PCr] (mM)</th>
<th>[Pi] (Mm)</th>
<th>pH</th>
<th>[ADP] (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older</td>
<td>Female</td>
<td>High</td>
<td>20.4±1.7*</td>
<td>2.6±0.2*</td>
<td>7.01±0.02</td>
<td>6.8±0.7</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Low</td>
<td>20.0±1.4*</td>
<td>2.1±0.2*</td>
<td>6.99±0.01</td>
<td>5.1±0.4*</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>High</td>
<td>22.1±1.4*</td>
<td>3.0±0.2*</td>
<td>7.03±0.01</td>
<td>7.4±0.6</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Low</td>
<td>23.8±1.7*</td>
<td>2.5±0.2*</td>
<td>6.99±0.02</td>
<td>5.5±0.6*</td>
</tr>
<tr>
<td>Younger</td>
<td>Female</td>
<td>High</td>
<td>29.9±1.0†</td>
<td>3.8±0.3</td>
<td>7.01±0.01</td>
<td>6.4±0.2</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Low</td>
<td>28.3±0.3†</td>
<td>3.1±0.5†</td>
<td>7.01±0.02</td>
<td>5.4±0.9†</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>High</td>
<td>32.1±2.7</td>
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<td>7.02±0.02</td>
<td>6.1±0.5</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Low</td>
<td>31.1±2.6</td>
<td>3.4±0.5†</td>
<td>7.02±0.01</td>
<td>5.7±0.6†</td>
</tr>
</tbody>
</table>

Data reported as means±SE for main effects from three-way ANOVA.

* $P \leq 0.05$ for age group differences (older < younger) differences.
† $P < 0.05$ for sex group differences (female < male).
‡ $P < 0.05$ for activity group differences (low < high).

Fig. 1. Box plots representing the relative distribution group magnetic resonance spectroscopy data for PDE resonance peak areas comparing older to younger subjects. Older subjects had significantly larger PDE peak resonance areas compared to younger subjects ($P < 0.05$).
paired, the changes in [PCr] and [ADP] are greater than normal (Kemp and Radda, 1994; Kemp et al., 1993; Taylor et al., 1997). Thus, the increased [ADP] that was demonstrated in the older subjects during both exercise and recovery would have been an appropriate response to maintain ATP production and to reduce a fall in pH in the face of mitochondrial impairment (Kemp and Radda, 1994; Kemp et al., 1993; Taylor et al., 1997).

In addition to a higher [ADP] response to exercise, and slower [ADP] and PCr recovery, the PDE peaks were also larger in our older subjects. This agrees with previous studies (Schunk et al., 1999; Taylor et al., 1997) and is believed to reflect the 'health' of the phospholipid membrane as well as acting as an indirect measure of oxidative stress on the mitochondrial membrane (Schunk et al., 1999; Taylor et al., 1997). Although we had no other measures of cellular oxidative stress, a relationship between cumulative oxidative damage to mtDNA and aging has been proposed by numerous investigators utilizing measures such as muscle biopsy (Papa and Skulachev, 1997; Wei et al., 1998; Weindruch, 1995; Zorov, 1996; Wanagat et al., 2001; Bua et al., 2002).

The hypothesis of cumulative oxidative damage has recently been strengthened by the works of Wanagat et al. (2001) in the rhesus monkey and rat demonstrating that mtDNA deletions accumulate with age and clonally accumulate within a small region of the muscle. The accumulation of abnormal mitochondria expanding along the length of the fiber produces an energy deficit reflected in the electron transport system, impaired cellular activity, and the ability to respond to physiological stress, which ultimately results in intrafiber atrophy (Wanagat et al., 2001). Furthermore, there is data to suggest that varying degrees of sarcopenia may coexist with varying degrees of mitochondrial dysfunction (Bua et al., 2002).

This would be in agreement with other studies that have reported differing rates in the loss muscle mass and quality in the lower body versus the upper body (Janssen

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Fig. 2. Group magnetic resonance spectroscopy data for older, male and female, high and low activity groups (panel A), and the younger, male and female, high and low activity groups (panel B), showing percentage of phosphocreatine (PCr) (% change PCR) during rest, 12 min of exercise, and 10 min of recovery. Minimum PCr was significantly lower (P = 0.01), and percentage change at end of exercise significantly higher (P = 0.02), in the older group.
et al., 2000; Lynch et al., 1999). In our study, older subjects had less lean body mass and appendicular skeletal muscle mass than the younger subjects despite even similar levels of physical activity. This was not expected as most studies report losses in lean body mass in both sedentary and active elderly older than 60 years of age (Baumgartner et al., 1998; Janssen et al., 2000; Proctor and Joyner, 1997). There is also evidence of denervation process, which would preferentially denature type II fibers (Doherty et al., 1993). The age-related loss of lean body mass can be attenuated with aging and the loss in the lower body Type II muscle fibers is not necessarily a consistent finding in older persons without a history of endurance training or physical activity (Fayet et al., 2001; Lynch et al., 1999). This appears to create a paradox, in that while exercise has many well known benefits on skeletal muscle, strenuous physical activity increases muscle oxygen flux and elicits intracellular events leading to oxidative damage. Moreover,

Table 3

<table>
<thead>
<tr>
<th>Age group</th>
<th>Sex group</th>
<th>Activity group</th>
<th>$t_{1/2}$ [ADP]</th>
<th>$t_{1/2}$ [PCr]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older</td>
<td>Female</td>
<td>High</td>
<td>44.0 ± 2.6*</td>
<td>48.8 ± 4.8</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Low</td>
<td>53.6 ± 5.2*</td>
<td>56.0 ± 5.0</td>
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<tr>
<td></td>
<td>Male</td>
<td>High</td>
<td>42.4 ± 5.6*</td>
<td>48.0 ± 3.4</td>
</tr>
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<td></td>
<td>Male</td>
<td>Low</td>
<td>54.6 ± 4.0*</td>
<td>44.9 ± 3.6</td>
</tr>
<tr>
<td>Younger</td>
<td>Female</td>
<td>High</td>
<td>29.0 ± 7.2</td>
<td>41.2 ± 9.2</td>
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<tr>
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<td>37.6 ± 4.4†</td>
<td>40.4 ± 4.6</td>
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<td>High</td>
<td>32.2 ± 3.0</td>
<td>56.8 ± 9.6*</td>
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<tr>
<td></td>
<td>Male</td>
<td>Low</td>
<td>40.0 ± 4.8*†</td>
<td>48.9 ± 8.0</td>
</tr>
</tbody>
</table>

Data expressed as means ± SE.
* $P < 0.05$ for age group differences (older > younger) differences.
† $P = 0.05$ for sex and age interaction.
‡ $P < 0.05$ for activity group differences (low > high). $t_{1/2}$ expressed in seconds.

Fig. 3. Group magnetic resonance spectroscopy data for older, male and female, high and low activity groups (panel A), and younger, male and female, high and low activity groups (panel B), showing percentage of [ADP] (% change [ADP]) during rest, 12 min of exercise and 10 min of recovery. Maximum [ADP] was significantly higher, and $t_{1/2}$ significantly longer in the older group overall ($P = 0.02$), and in the older low activity group compared to the older high activity group ($P = 0.04$).
increasing age is associated with increased free radical generation in skeletal muscle and a reduced capacity for repair and regeneration potentially enhancing the accrual of oxidative damage, mtDNA damage, and mitochondrial dysfunction (Ji, 2001).

A decline in mitochondrial function with aging has been reported by some (Conley et al., 2000; Kemp and Radda, 1994; Kemp et al., 1993; Taylor et al., 1997), although refuted by others who propose that decreasing mitochondrial function in aging can be attenuated with exercise training (Brierly et al., 1997a, 1996, 1997b; Kent-Braun and Ng, 2000; McCully et al., 1991). This premise, although appealing is difficult to reconcile with changes in aging muscle that make it more susceptible to oxidative damage, and the body of evidence reporting declining VO_{2max} and mitochondrial function with age in competitive older athletes (Conley et al., 2000; Dempsey and Seals, 1995; Hawkings et al., 2001; Katzel et al., 2001). Proctor and Joyner (1997) reported a decline in VO_{2} max per kilogram limb muscle in highly trained men and women relative to their younger counterparts and suggested that this loss was due to the reduced aerobic capacity per kilogram of active muscle independent of age-related changes in body composition. Although they did not obtain muscle biopsies in this study, they speculated that the reduced aerobic capacity could reflect reduced O_{2} extraction by active muscles and/or reduced O_{2} delivery to the active muscle secondary to decreased maximal cardiac output. The dependence of phosphocreatine recovery from exercise on O_{2} availability was also reported by Haseler et al. (1999) in healthy, untrained younger men. They reported that maximal mitochondrial respiratory rate is dependent on substrate availability including not only O_{2}, but also ADP, Pi, NAD+/NADH. Finally, the accumulation of red ragged fibers and abnormal mitochondria in concert with the loss of oxidative capacity in aged muscle also provides indirect evidence of oxidative stress and mtDNA damage (Fayet et al., 2001).

5. Conclusions

We conclude from the results of this study, that there is a age-related decline in mitochondrial function in healthy exercising elderly which appears somewhat attenuated by higher levels of physical activity. Other factors such as changes in mRNA, protein synthesis, muscle quality, enzymes, membrane potential, cardiac output and O_{2} extraction could also be involved (Dempsey and Seals, 1995; Doherty et al., 1993; Fayet et al., 2001; Kirkeby and Grbarsch, 2000; Klitgaard et al., 1990; Navarro et al., 2001; Vandervoort, 2002). Longitudinal studies of the long-term effects of varied levels of physical activity on muscle fibers, oxidative stress, and mitochondrial function are needed before this complex, multi-factorial question of mitochondrial decline with aging can be answered.

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