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Skeletal Muscle Mitochondrial Energetics Are Associated With Maximal Aerobic Capacity and Walking Speed in Older Adults

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Background. Lower ambulatory performance with aging may be related to a reduced oxidative capacity within skeletal muscle. This study examined the associations between skeletal muscle mitochondrial capacity and efficiency with walking performance in a group of older adults.

Methods. Thirty-seven older adults (mean age 78 years; 21 men and 16 women) completed an aerobic capacity (VO₂ peak) test and measurement of preferred walking speed over 400 m. Maximal coupled (State 3; St3) mitochondrial respiration was determined by high-resolution respirometry in saponin-permeabilized myofibers obtained from percutaneous biopsies of vastus lateralis ($n = 22$). Maximal phosphorylation capacity (ATP_{max}) of vastus lateralis was determined in vivo by ³¹P magnetic resonance spectroscopy ($n = 30$). Quadriceps contractile volume was determined by magnetic resonance imaging. Mitochondrial efficiency (max ATP production/max O₂ consumption) was characterized using ATP_{max} per St3 respiration (ATP_{max}/St3).

Results. In vitro St3 respiration was significantly correlated with in vivo ATP_{max} ($r^2 = .47, p = .004$). Total oxidative capacity of the quadriceps (St3*quadriceps contractile volume) was a determinant of VO₂ peak ($r^2 = .33, p = .006$). ATP_{max} ($r^2 = .158, p = .03$) and VO₂ peak ($r^2 = .475, p < .0001$) were correlated with preferred walking speed. Inclusion of both ATP_{max}/St3 and VO₂ peak in a multiple linear regression model improved the prediction of preferred walking speed ($r^2 = .647, p < .0001$), suggesting that mitochondrial efficiency is an important determinant for preferred walking speed.

Conclusions. Lower mitochondrial capacity and efficiency were both associated with slower walking speed within a group of older participants with a wide range of function. In addition to aerobic capacity, lower mitochondrial capacity and efficiency likely play roles in slowing gait speed with age.

Key Words: Muscle—Mitochondria—Aging—Walking speed.

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AGING is associated with reduced mitochondrial capacity (1,2) and loss of muscle mass and strength (3,4), which could potentially predispose individuals to frailty and a slower preferential walking speed (5,6). Preferred walking speed is slower in older adults (7,8), and is a strong, independent predictor of disability, health care utilization, nursing home admission, and mortality (9–11). A number of studies have found a close relationship between VO₂ peak and walking speed in older adults (12,13), which

suggests that the decline in aerobic capacity contributes to, and may be predictive of, slower walking speed with age. A reduced efficiency of locomotion is also apparent in older adults, which leads to an increased metabolic cost of walking (14).

Aging is also associated with declines in both the capacity and efficiency of energy supply in muscle. Several studies using a variety of techniques have reported reduced capacity to generate ATP with age (1,15,16). The age-related changes

in skeletal muscle mitochondrial function apparent in these studies are consistent with their likely role in the parallel loss of aerobic capacity (1,16). In addition, reduced mitochondrial efficiency (energy conversion of O_2 uptake into ATP generation) has been reported in a variety of tissues in vitro and in vivo (17–19). The importance of mitochondrial efficiency is that it could affect the ability to generate ATP during ambulation (16) as well as movement efficiency (20–22). One study found that walking speed in patients with peripheral arterial disease was related to their capacity for ATP generation assessed by phosphorus magnetic resonance spectroscopy (^{31}P MRS) (23). Although the loss of muscle mitochondrial function has been widely hypothesized to contribute to the decline in VO_2 max and slowing of locomotion with age, there currently is insufficient published evidence to show that reductions in available energy results in a decline in customary walking speed with aging and disease (11). Furthermore, the potential role of mitochondrial efficiency in energy availability for walking has not been examined.

The goal of this study was to test the hypothesis that reduced mitochondrial capacity and efficiency are associated with slower walking speed in older adults. In vitro (respirometry) and in vivo (^{31}P MRS) measurements of mitochondrial function were combined and related to whole-body aerobic capacity (VO_2 peak) and preferred walking speed in a group of older men and women. High-resolution respirometry of permeabilized fibers isolated from muscle biopsy specimens yielded mitochondrial oxidative capacity (State 3 or St3 respiration). These measures of mitochondrial capacity at cellular level were extended to the muscle tissue level by assessing quadriceps muscle volume with magnetic resonance imaging (MRI). ^{31}P MRS was used to determine the maximum mitochondrial ATP production (ATP_{max}) in vivo, which was combined with St3 respiration to yield an index of mitochondrial efficiency ($ATP_{max}/St3$). This study tested the paradigm that muscle mitochondrial properties affect walking speed and that mitochondria capacity and efficiency may be associated with the decline in mobility with age (Figure 1).

METHODS

Recruitment

Participants were community-dwelling, ambulatory men and women aged 70–89 years from the Pittsburgh, Pennsylvania area. A telephone interview was initially conducted to determine eligibility. The inclusion criteria were age 70–89 years; body weight less than or equal to 285 lb for men and less than or equal to 250 lb for women; body mass index 20–32 kg/m²; ability to walk without the assistance of a device or another person; free of basic activities of daily living disability, defined as no difficulty getting in and out of bed or chairs, and no difficulty walking across a small room; no history of hip fracture; no heart attack,

angioplasty, or heart surgery within the past 3 months, no cerebral hemorrhage within the past 6 months, stroke within the past 12 months, or chest pain during walking in the past 30 days; no symptomatic cardiovascular or pulmonary disease; no regular pain, aching, or stiffness in the legs, hips, knees, feet, or ankles when walking; no bilateral difficulty bending or straightening fully the knees; not regularly taking Coumadin, Plavix, Aggrenox, Ticlid, or Agrylin/Xagrid. All participants provided written informed consent. The study was approved by the University of Pittsburgh Institutional Review Board.

Testing Schedule

The clinic examination involved three visits. During the first visit potential participants were asked to read and sign an informed consent document. Measurements included height, weight, blood pressure, and resting pulse. A physical examination was also conducted along with a review of clinical information including self-reported physical function, medical history, and medication inventory. A physical activity scale for the elderly questionnaire was completed and a final summary score was calculated (24). A short physical performance battery was conducted and an overall score was calculated (25). A 400-m walk test was conducted to determine self-selected walking speed. Participants were also given a 5-minute practice session on the treadmill to become acquainted with treadmill walking prior to the VO_2 peak test conducted in a subsequent visit. The second visit involved ^{31}P MRS and imaging and a graded exercise test to determine VO_2 peak. The third visit involved muscle tissue collection.

The 400-m Walk Test

The 400-m walk test assessed the participant's ability to complete a 400-m walking course in 15 minutes or less without sitting down or stopping, without help, or the use of any assistive device. Participants were instructed to complete the distance at their usual pace and without overexerting themselves. Participants were reminded to walk at their usual pace every lap. Seated blood pressure and pulse were reviewed for safety before the walk. Preferred walking speed was calculated as total meters walked/total time in seconds.

VO_2 Peak Test

Maximal whole-body oxygen consumption (VO_2 peak) was determined by a graded treadmill exercise test (26). A resting 12-lead electrocardiogram was conducted prior to the VO_2 peak test to screen for cardiac arrhythmias. To ensure participant safety, continuous electrocardiogram monitoring was also performed during the VO_2 peak test. During the test, the participant's self-selected usual walking speed was used and the treadmill grade was increased by 2% every 2 minutes until attainment of peak VO_2 . The test

was terminated as per the criteria outlined in the American College of Sports Medicine guidelines (26).

Muscle Biopsy Procedure and Preparation of Permeabilized Muscle Fiber Bundle

Percutaneous biopsies were obtained at the University of Pittsburgh's Clinical Translational Research Center on a morning after an overnight fast. Participants were instructed not to perform physical exercise 48 hours prior to the muscle biopsy procedure. Muscle biopsy samples were obtained from the middle region of the musculus vastus lateralis as described previously (27). Following the procedure, the biopsy specimen was immediately blotted dry of blood and interstitial fluid and dissected free of any connective tissue and intermuscular fat. A portion of the biopsy specimen (~10 mg) was immediately placed in ice-cold BIOPS solution (10 mM Ca-EGTA buffer, 0.1 M free calcium, 20 mM imidazole, 20 mM taurine, 50 mM potassium 2-[N-morpholino]-ethanesulfonic acid, 0.5 mM dithiothreitol, 6.56 mM MgCl₂, 5.77 mM ATP, and 15 mM phosphocreatine [PCr], pH 7.1). The individual muscle fibers in the sample were then gently teased apart in a petri dish containing ice-cold BIOPS solution using fine-nosed forceps and a dissecting microscope (Leica Microsystems, Heerbrugg, Switzerland). The fiber bundles were then permeabilized with saponin (2 mL of 50 µg/mL saponin in BIOPS solution) for 20 minutes at 4°C on an orbital shaker, and then washed twice for 10 minutes at 4°C with Mir05 respiration medium (0.5 mM EGTA, 3 mM MgCl₂·6H₂O, 60 mM K-lactobionate, 20 mM taurine, 10 mM KH₂PO₄, 20 mM HEPES, 110 mM sucrose, and 1 g/L BSA, pH 7.1) on an orbital shaker (28). The permeabilized muscle fiber bundles were then placed into the respiration chambers of an Oxygraph 2K (Oroboros Inc., Innsbruck, Austria).

Mitochondrial Respiration Protocol

Measurement of oxygen consumption in permeabilized fibers was conducted over a period of approximately 1 hour 40 minutes, at 37°C and in the oxygen concentration range 220–150 nmol O₂/mL (see [Supplementary Method](#) for full protocol). Following the assay, the fiber bundles were recovered and dried. A dry weight was then determined with an analytical balance (Mettler Toledo, XS105). Steady state O₂ flux for each respiratory state was determined and normalized to fiber bundle weight using Datlab 4 software (Oroboros Inc.).

Determination of ATP_{max} by ³¹P MRS

Maximal mitochondrial ATP production in vivo (ATP_{max}) following an acute bout of knee extensor exercise was determined using ³¹P MRS. Recovery of PCr levels after exercise is used to characterize rates of mitochondrial ATP resynthesis (production). The validity of this method

is confirmed by animal and human studies showing that ATP_{max} varies in direct proportion to the oxidative enzyme activity of healthy muscle (29,30) and corresponds with mitochondrial content in human muscle (16). Repeat measurements of muscle ATP_{max} have been shown to agree to within about 7% (31).

Exercise Protocol

The exercise protocol was designed to deplete PCr of the quadriceps muscles with minimal acidification to achieve a high ADP and thus maximize oxidative phosphorylation (30). Participants lay supine in the scanner's bore with the knee supported in about 30° of flexion. Sandbags and padding were placed on both sides of the ankle and knee for support and straps placed across the distal leg, thigh, and hips restricted limb movement. Participants performed strong, fast contractions of the quadriceps muscle at the highest rate possible for 24–36 seconds, followed by 6 minutes of rest. Most participants repeated this protocol twice, with two different exercise times, to ensure that in at least one bout PCr was reduced by 33%–66% of basal and that muscle pH did not fall less than 6.80 during recovery. Participants were trained to perform the exercise before entering the magnet.

³¹P MRS

Phosphorus spectra was collected using a 3T TIM Trio magnetic resonance scanner (Siemen's Medical System, Erlanger, Germany) (see [Supplementary Method](#)). A standard one pulse experiment was used to determine the levels of PCr, ATP, P_i, and pH throughout exercise and recovery.

PCr, P_i, and ATP peak areas in the fully relaxed spectra were measured by integration using Varian VNMR 6.1C software (Varian Medical Systems, Palo Alto, CA). Areas of the PCr and P_i peaks were expressed relative to the ATP peak and quantified using a resting PCr value of 27 mM as determined from biopsies of human vastus lateralis muscle (16). Changes in PCr and P_i peak areas during the experiments were analyzed as previously described (32,33).

Determination of Muscle Size

MRI was used to determine quadriceps cross-sectional area and volume according to a previously described method (see [Supplementary Method](#)) (35). Using a 3T TIM Trio magnetic resonance scanner (Siemen's Medical System), images were collected every 3 cm from the hip to the thigh (15–25 slices per participant). The patient lay supine for imaging. Standard stereologic techniques were used to determine the largest muscle cross-sectional area for the quadriceps (35). Subcutaneous and intramuscular fat and other noncontractile tissues were excluded from the calculation of muscle contractile cross-sectional area.

Statistical Analysis

All data are presented as mean \pm SD unless otherwise stated. Pearson correlation coefficients were used to examine relationships between variables. A multiple linear regression model was used to predict preferred walking speed from VO_2 peak and mitochondrial efficiency ($\text{ATP}_{\text{max}}/\text{St3}$ respiration).

RESULTS

Participant Characteristics

A total of 179 potential participants were screened by telephone interview. Of those interviewed, 99 individuals were ineligible and 43 were not interested in participating. A total of 37 older adults (21 men and 16 women); who were normal weight to slightly overweight were studied (Table 1). The group had on average a relatively low and widely ranging level of aerobic fitness defined by VO_2 peak (Table 1). This group of older participants also had a fairly wide range of preferred walking speed, and the short physical performance battery scores were indicative of low to moderate lower extremity function (Table 1).

Muscle Magnetic Resonance Measurements

Due to exclusions from MRI, for example, history of metal work or claustrophobia, a subsample of individuals ($n = 30$; 16 men and 14 women) had ATP_{max} determined by ^{31}P MRS. The average ATP resynthesis rate (ATP_{max}) was 0.52 mM ATP/s and covered a greater than 2.5-fold range (0.32–0.83) in agreement with reports on older adults (16). The quadriceps contractile muscle size determined from MRI was also consistent with values previously reported for older participants (36). The coefficient of variation for repeat determinations on 8 participants was 7.2% for ATP_{max} , and 3% for quadriceps volume.

Respirometry Measurements

A subsample of individuals ($n = 22$; 12 men and 10 women) had muscle biopsies that were studied by high-resolution respirometry. The maximal coupled respiratory capacity (St3 respiration) of vastus lateralis–permeabilized fiber bundles ranged greater than fivefold (Table 1). The nonphosphorylating rate of respiration (State 4 or St4 respiration) displayed a similar wide range as St3. A respiratory control ratio (St3/St4) of 11.8 indicated good preparation of permeabilized muscle fiber bundles (37). These data are in agreement with previous respirometry measurements on permeabilized fibers from older adults (75 years old) with St3 and St4 respiration averaging 199 and 24 $\text{pmol/s}^{-1}\text{mg DW}$, respectively, based on Figure 1 from reference (38) and the conversion ratio of wet-to-dry weight from reference (39). The coefficient of variation of the respirometry assay for this study was determined to be 16.9% (St3 respiration, determined from 6 participants). A representative oxygraph is presented in Supplementary Figure 1.

Associations Among In Vitro and In Vivo Muscle and Whole-Body Oxidative Capacity

Maximal coupled, St3 respiration ($r^2 = .47$, $p = .004$; Figure 2), and maximal uncoupled respiration ($r^2 = .47$, $p = .002$; Supplementary Table 1) measured in intact muscle fibers from the biopsy were significantly correlated with whole-muscle ATP_{max} , indicating a close relationship between the measurements of oxidative capacity of permeabilized fibers and phosphorylation capacity of intact muscle.

The relationship of muscle respiratory and oxidative capacity to whole-body aerobic capacity was evaluated by combining respirometry data and MRI measurements of quadriceps contractile volume. A measure of muscle oxidative capacity was derived from the product of St3 respiration and the volume of quadriceps muscle ($\text{St3} \cdot V_Q$). Figure 3 shows that variation in VO_2 peak is significantly

Table 1. Descriptive, Metabolic and Physiological Data for Study Participants

<i>n</i>	37 (M = 21, F = 16)
Age (y)	78.3 \pm 4.9 (60–89)
Weight (Kg)	72.0 \pm 12 (53–97)
BMI (Kg/m ²)	25.7 \pm 2.6 (21.4–31.2)
Quadriceps contractile volume (mL)	1159 \pm 324 (589–1886), <i>n</i> = 30
ATP_{max} (mM ATP/s)	0.52 \pm 0.1 (0.32–0.83), <i>n</i> = 30
State 3 respiration (pmol/s*mg DW)	174 \pm 68 (52–303), <i>n</i> = 22
State 4 respiration (pmol/s*mg DW)	16.4 \pm 7.1 (4.0–30.8), <i>n</i> = 22
Respiratory control ratio	11.8 \pm 5.1 (6.1–26), <i>n</i> = 22
Mitochondrial efficiency; $\text{ATP}_{\text{max}}/\text{State 3 respiration}$ ((mM ATP/s)/(pmol O ₂ /s*mg DW))	3.5 \pm 1.7 $\times 10^3$ (1.8 $\times 10^3$ –7.9 $\times 10^3$), <i>n</i> = 18
Quadriceps oxidative capacity; State 3 respiration \times muscle volume ((pmol O ₂ /s*mg DW)*mL muscle)	209 \pm 89.4 $\times 10^3$ (78 $\times 10^3$ –488 $\times 10^3$), <i>n</i> = 22
VO_2 peak (mL/min)	1551.5 \pm 408 (750–2724)
VO_2 peak (mL/KgBW/min)	22.0 \pm 5.5 (7.8–33.4)
Preferred walking speed over 400 m (m/s)	1.2 \pm 0.2 (0.74–1.58)
SPPB score	10.9 \pm 1.3 (7–12)
PASE score	133 \pm 55 (15–274)

Notes: Values are average \pm SD (Min-Max). BMI = body mass index; BW = body weight; DW = dry weight of tissue; PASE = physical activity scale for the elderly participants; SPPB = short performance physical battery.

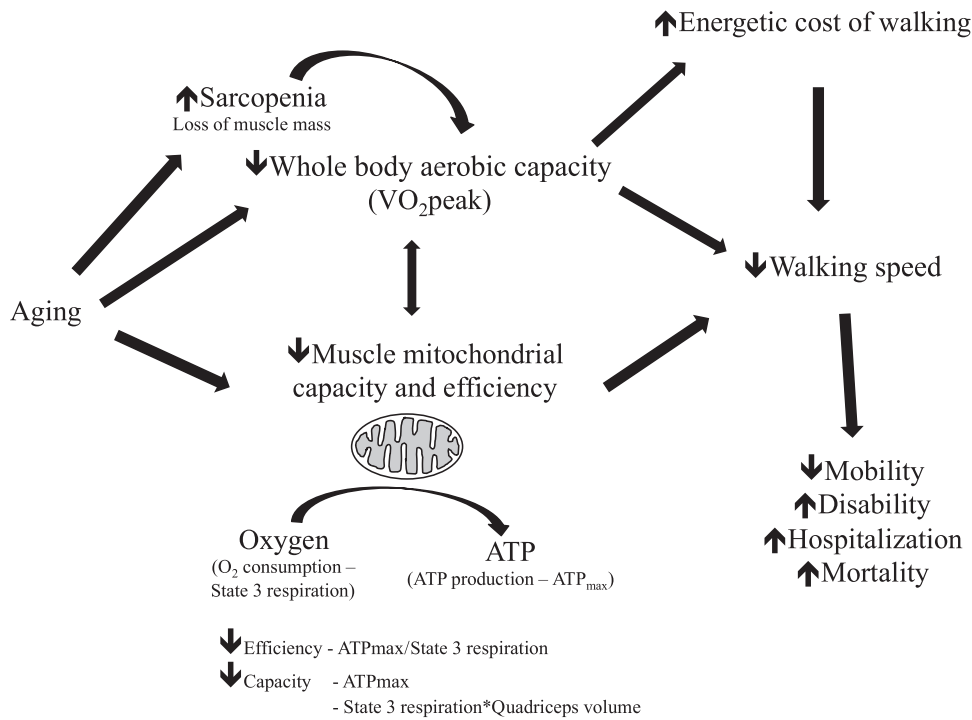


Figure 1. Concept map illustrating age-related changes in muscle physiology and how they contribute to reduced walking speed in older adults. This study examined the relationships between muscle mitochondrial capacity/efficiency, aerobic capacity, and walking speed in older adults. VO_2 peak = maximal oxygen consumption during maximal dynamic exercise. This is an index of whole-body aerobic capacity.

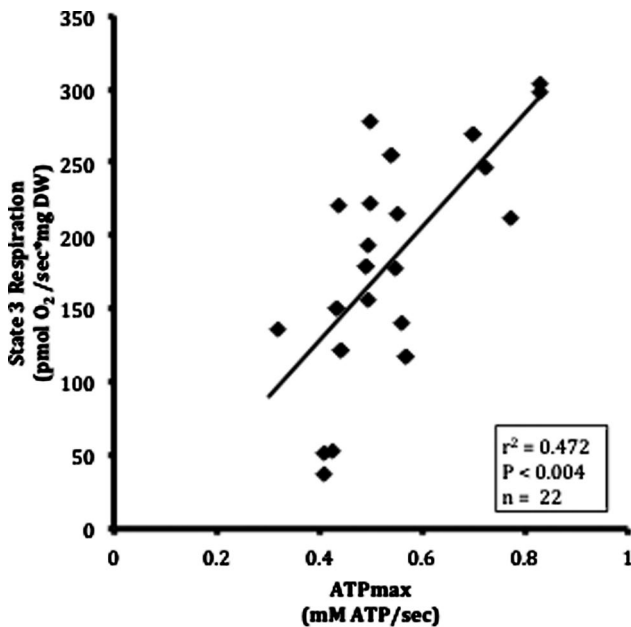


Figure 2. Pearson correlation of maximum respiratory capacity with maximum oxidative phosphorylation in muscle. State 3 respiration in permeabilized fiber bundles was determined by high-resolution respirometry. Maximum oxidative phosphorylation (ATP_{max}) elicited by exercise was determined by phosphorus magnetic resonance spectroscopy (31P MRS). DW = dry weight.

correlated with the quadriceps' oxidative capacity ($r^2 = .33$, $p < .0061$). These associations were consistent for both men and women. This finding is also consistent with a prior study in older adults (36).

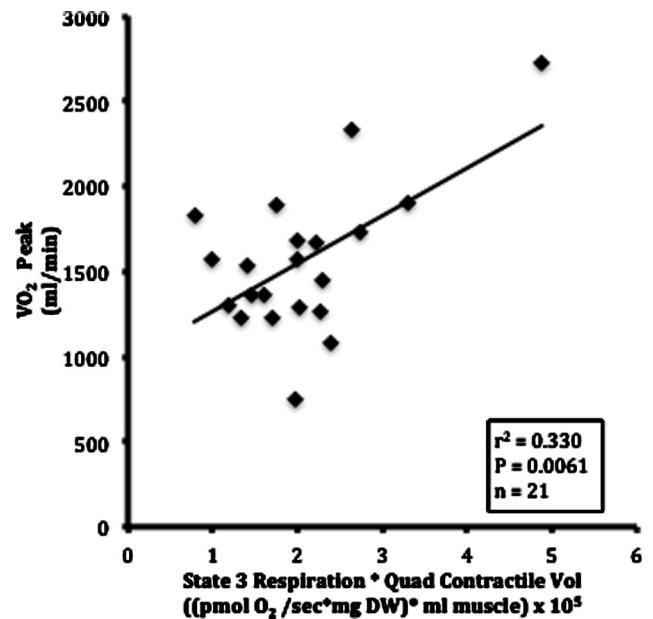


Figure 3. Pearson correlation of whole-body aerobic capacity with muscle oxidative capacity. Aerobic capacity (VO_2 peak) was determined by a graded exercise test. Muscle oxidative capacity was defined as the product of State 3 respiration and quadriceps contractile volume (State 3 respiration * quadriceps contractile volume). DW = dry weight.

The Impact of Energetics on Walking Speed

The range of VO_2 peak among participants accounted for 48% of the variation in preferred walking speed over 400 m (Figure 4, Panel A: $r^2 = .48$, $p < .0001$), in agreement with

previous studies of energetics in older adults (12,13). It was also found that ATP_{max} accounted for 15.8% of the variation in preferred walking speed (Figure 4, Panel B: $r^2 = .158$, $p = .03$). The impact of mitochondrial efficiency ($ATP_{max}/St3$) on the relationship between aerobic capacity (VO_2 peak) and walking performance was tested using a multiple linear regression model. Table 2 shows that independent of VO_2 peak, mitochondrial efficiency was borderline associated with preferred walking speed ($ATP_{max}/St3$; $p = .057$). Together, however, VO_2 peak and $ATP_{max}/St3$ predicted approximately 65% of the variation in preferred walking speed (Figure 5, $r^2 = .647$, $p < .0001$) as compared with 47.5% of the variation by VO_2 peak alone. Adding gender to the model did not significantly affect these associations. The correlations between all respirometry states, MRS, VO_2 peak, and walking speed are presented in Supplementary Table 1.

DISCUSSION

This study provides novel evidence obtained at the cellular, tissue, and whole-body level that skeletal muscle mitochondrial capacity and efficiency are associated with preferred walking speed in older men and women. First, it was found that muscle oxidative and phosphorylation capacities, whole-body aerobic capacity, and walking speed all varied manifold among older adults in accordance with their fairly broad range in function. Second, muscle mitochondrial capacity and efficiency along with whole-body aerobic capacity were directly associated with walking speed. Aerobic capacity (VO_2 peak) varied in proportion to muscle respiratory capacity as measured by St3 respiration (oxidative capacity) of permeabilized fibers combined with quadriceps volume (Figure 3). Aerobic capacity and mitochondrial capacity were also strongly correlated with walking speed (Figure 4). The third key finding was that muscle mitochondrial efficiency ($ATP_{max}/St3$) provided independent explanatory power to predict walking speed, additional to that provided by VO_2 peak alone. These data indicate that muscle mitochondrial capacity and efficiency are associated with ambulatory performance of older adults.

Mitochondrial Capacity of Muscle Fibers

Firstly, mitochondrial respiratory capacity determined from permeabilized muscle fibers was compared to phosphorylation capacity of whole muscle. It was found that St3 respiration was directly proportional to ATP_{max} over the manifold range of properties found among these participants. Thus, a higher oxidative capacity of the muscle fiber is reflected in a higher oxidative phosphorylation capacity in whole muscle. This finding is in agreement with studies correlating mitochondrial content and enzymatic activity of muscle biopsies with ATP_{max} (16,29). Thus, for the first time two separate measures of muscle mitochondrial energetics,

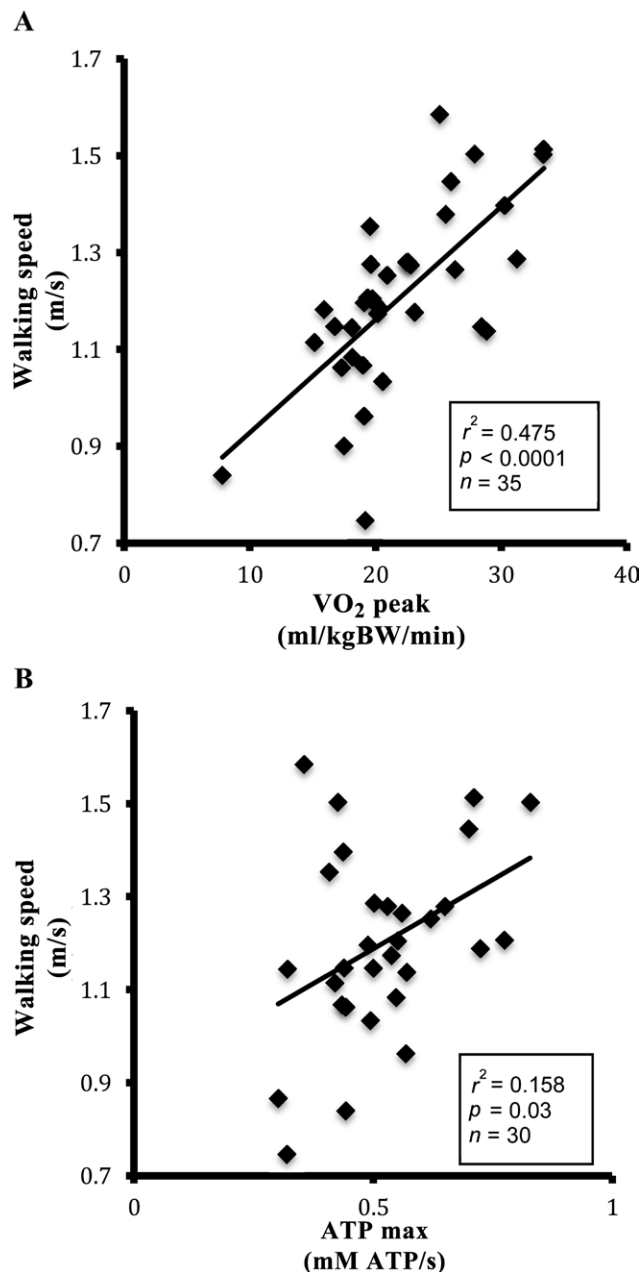


Figure 4. Pearson correlation of preferred walking speed with whole-body aerobic capacity and muscle mitochondrial capacity. Panel (A): preferred walking speed versus VO_2 peak. Panel (B): preferred walking speed versus ATP_{max} . Aerobic capacity normalized to body weight (mL/kgBW/min) was determined by a graded exercise test. Preferred walking speed was determined over a 400-m walk test. ATP_{max} was determined by ^{31}P magnetic resonance spectroscopy.

determined in vitro by respirometry and in vivo by ^{31}P MRS in older adults, show a correspondence between mitochondrial respiratory capacity and whole-muscle phosphorylation capacity.

Impact of Metabolic Capacity and Efficiency on Mobility

A key question of this study was whether—and the extent to which—metabolic capacity and efficiency are related to

Table 2. Multiple Linear Regression for the Model of Preferred Walking Speed as a Function of Aerobic Capacity Per Body Mass (VO_2 peak; mL/kgBW/min) and Mitochondrial Efficiency ($\text{ATP}_{\text{max}}/\text{State 3}$)

Analysis of Variance				
Variable	Coefficient	SE	F Value	p Value
Intercept	0.4561	0.143	10.11	.0062
$\text{ATP}_{\text{max}}/\text{State 3}$	37.786	18.3	4.26	.0567
VO_2 peak	0.0272	0.005	24.18	.0002
Summary of Stepwise Selection				
Step	Variable entered	Partial R-squared	Model R-squared	
1	VO_2 peak	0.4753	0.4753	
2	$\text{ATP}_{\text{max}}/\text{State 3}$	0.1714	0.6467	

Note: SE = standard error.

walking performance. The hypothesis that walking speed is not only affected by whole-body aerobic capacity (VO_2 peak) but also by muscle mitochondrial efficiency ($\text{ATP}_{\text{max}}/\text{St3}$) was tested. The contribution of both aerobic capacity and mitochondrial efficiency on walking speed is apparent in the multiple linear regression model shown in Table 2. In this model, the positive coefficient for VO_2 peak implies that a higher aerobic capacity is associated with a faster preferred walking speed. Similarly, the positive coefficient for $\text{ATP}_{\text{max}}/\text{St3}$ implies that greater mitochondrial efficiency has a beneficial effect on walking speed. Together, aerobic capacity and mitochondria efficiency accounted for 64.7% of the variation in walking speed, whereas VO_2 peak alone accounted for only 47.5% of the variation. The contribution of mitochondrial efficiency, independent of VO_2 peak, can be further highlighted by examining data from individual participants. For example, for 2 participants with similar VO_2 peaks, 1 participant had a higher walking speed (1.5 m/s) and high mitochondrial efficiency (7.9×10^3 [mM ATP/s]/[pmol $\text{O}_2/\text{s} \cdot \text{mg DW}$]), whereas the second had a lower walking speed (0.74 m/s) and low mitochondrial efficiency (2.3×10^3 [mM ATP/s]/[pmol $\text{O}_2/\text{s} \cdot \text{mg DW}$]). Alterations in mitochondrial efficiency of ATP production may be caused by reduced inner mitochondrial membrane leak or by reduced electron leak from the electron transport chain. Further studies are warranted to determine the causal factors mediating muscle mitochondrial efficiency in older adults. This is the first study, to the authors' knowledge, to demonstrate that greater muscle mitochondrial efficiency may play a direct role in gait speed in older adults.

Muscle Impact on Metabolic Capacity

Here, mitochondrial respiratory capacity (St3) was combined with quadriceps contractile volume (V_Q) to extend the oxidative capacity of the muscle fibers to that of the whole quadriceps. It was found that the oxidative capacity of the quadriceps accounted for 33% of the variation in VO_2 peak (Figure 3), a finding that is in agreement with a prior study of individuals 20–80 years old (36). This agreement suggests that mitochondria play

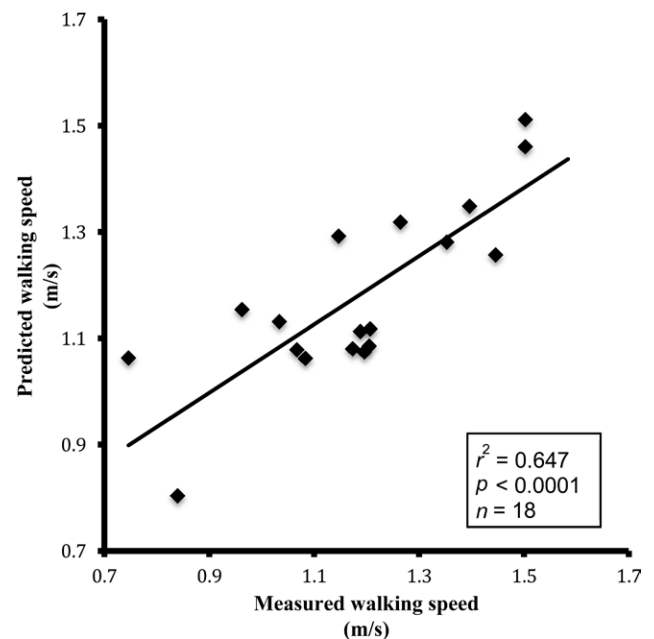


Figure 5. Pearson correlation of predicted preferred walking speed versus measured preferred walking speed. Walking speed was predicted from aerobic capacity (VO_2 peak) and muscle mitochondrial efficiency ($\text{ATP}_{\text{max}}/\text{State 3}$) by multiple linear regression (Table 2). Measured preferred walking speed was determined over a 400-m walk test.

an important role in determining cardiorespiratory fitness in older individuals. In contrast, a study of young and master endurance-trained athletes concluded that cardiac output and O_2 delivery to the muscle likely sets the limits to the aerobic capacity (40). These highly active older adults may well have reached the limits to oxygen delivery, as found in younger athletes (average age: 26.1 years old) (41). However, direct measurements demonstrating an O_2 delivery limit in athletic individuals (41) fail to find a similar limitation in more sedentary people (42). The lack of O_2 delivery limitation in less active older participants is evident in the scaling of maximum O_2 uptake in proportion to the muscle's capacity for O_2 consumption in older adults that is apparent in Figure 3 and reported previously (36). These data indicate that in nonathletic older participants with a wide variation in physical function, muscle

mitochondrial capacity is an important factor in addition to the cardiovascular system in determining VO_2 peak across age. Thus, these data suggest that interventions to enhance muscle mitochondria could have important effects to improve exercise tolerance and function in relatively sedentary older adults.

There are some potential limitations and caveats to this study. Firstly, the strong relationship between VO_2 peak and quadriceps oxidative capacity (Figure 3) is dependent on one or two data points. A larger study with more participants would provide a more definitive view of this relationship. Secondly, although the range of functional performance of older adult participants was fairly broad, this study included few very low functioning people. Inclusion of more very low functioning older adults may have further strengthened the observed relationships between muscle mitochondrial capacity/efficiency and gait speed. Nevertheless, it is believed that these findings may be clinically relevant, because walking speed has recently been identified as an important determinant of health and mortality in older men and women (9,10). Thirdly, despite the lack of significant gender effect on these associations, this study was not adequately powered to examine gender-specific associations. Thus larger studies are warranted to determine whether mitochondrial energetics are more or less strongly associated with function in men and women specifically.

In conclusion, muscle mitochondrial capacity and efficiency are related to walking speed in older adults, and that the loss of mitochondrial capacity and efficiency with age may be important contributors to the reduction in mobility and increase in disability. Future prospective longitudinal studies should determine whether mitochondrial energetics predict the decline in walking speed and function as well as incident mobility limitations.

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SUPPLEMENTARY MATERIAL

Supplementary material can be found at: <http://biomedgerontology.oxfordjournals.org/>

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