

## Ageing, muscle properties and maximal O<sub>2</sub> uptake rate in humans

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1. This paper asks how the decline in maximal O<sub>2</sub> uptake rate ( $\dot{V}_{O_{2,max}}$ ) with age is related to the properties of a key muscle group involved in physical activity – the quadriceps muscles. Maximal oxygen consumption on a cycle ergometer was examined in nine adult (mean age 38.8 years) and 39 elderly subjects (mean age 68.8 years) and compared with the oxidative capacity and volume of the quadriceps.
2.  $\dot{V}_{O_{2,max}}$  declined with age between 25 and 80 years and the increment in oxygen consumption from unloaded cycling to  $\dot{V}_{O_{2,max}}$  ( $\Delta\dot{V}_{O_2}$ ) in the elderly was 45% of the adult value.
3. The cross-sectional areas of the primary muscles involved in cycling – the hamstrings, gluteus maximus and quadriceps – were all lower in the elderly group. The quadriceps volume was reduced in the elderly to 67% of the adult value. Oxidative capacity per quadriceps volume was reduced to 53% of the adult value. The product of oxidative capacity and muscle volume – the quadriceps oxidative capacity – was 36% of the adult value in the elderly.
4. Quadriceps oxidative capacity was linearly correlated with  $\Delta\dot{V}_{O_2}$  among the subjects with the slope indicating that the quadriceps represented 36% of the  $\dot{V}_{O_2}$  increase during cycling.
5. The decline in quadriceps oxidative capacity with age resulted from reductions in both muscle volume and oxidative capacity per volume in the elderly and appears to be an important determinant of the age-related reduction in  $\Delta\dot{V}_{O_2}$  and  $\dot{V}_{O_{2,max}}$  found in this study.

Aerobic performance declines with age as shown by the decline in oxygen uptake and power output by the legs at maximal oxygen uptake rate ( $\dot{V}_{O_{2,max}}$ ) (Coggan *et al.* 1993; McCully *et al.* 1993; Proctor & Joyner, 1997). Cardiovascular limitations have been suggested to account for the decline in  $\dot{V}_{O_{2,max}}$  with age in trained subjects based on a reduction in the elderly of blood flow during submaximal exercise (see Proctor *et al.* 1998) and in  $\dot{V}_{O_{2,max}}$  per muscle volume (Proctor & Joyner, 1997). However, Seals *et al.* (1984) found an increase in  $\dot{V}_{O_{2,max}}$  in previously untrained subjects after endurance training without apparent increase in cardiac output. This result suggests that the peripheral capacity for oxygen consumption in untrained elderly subjects is important in addition to central cardiovascular factors in the age-related drop in aerobic performance.

Evidence for the role of the muscles themselves in the reduction in  $\dot{V}_{O_{2,max}}$  is muscle atrophy (Conley *et al.* 1995; Fleg & Lakatta, 1988; Frontera *et al.* 1991; Phillips *et al.* 1992; Proctor & Joyner, 1997) and the reduction in oxidative properties with age (Houmard *et al.* 1998). Recent *in vivo* measurements of whole muscle by magnetic resonance (MR) indicate significant age-related declines in oxidative

properties per muscle volume (Coggan *et al.* 1993; McCully *et al.* 1993; Conley *et al.* 2000). These *in vivo* whole muscle determinations point to a significant loss of muscle oxidative capacity that, combined with the observed reduction in muscle mass, may account for the reduction in  $\dot{V}_{O_{2,max}}$  with age.

The purpose of this study was to determine how the decline in  $\dot{V}_{O_{2,max}}$  is related to the changes in muscle properties with age. A maximal aerobic test on a cycle ergometer was used to determine  $\dot{V}_{O_{2,max}}$ . Magnetic resonance was used to determine the *in vivo* size and oxidative capacity of the quadriceps muscle. These measurements were used to determine the contributions of muscle size and oxidative capacity to the age-related reduction in  $\dot{V}_{O_{2,max}}$ .

## METHODS

### Subjects

The subjects' characteristics and magnetic resonance methods have been reported in the accompanying paper (Conley *et al.* 2000). Briefly, the adult group consisted of nine subjects (6 males, 3 females; aged  $38.8 \pm 7.9$  years, mean  $\pm$  s.d.) and the elderly group

Table 1. Oxygen uptake in the aerobic performance test

Group	Age (years)	$\dot{V}_{O_2,rest}$ (ml min <sup>-1</sup> )	$\dot{V}_{O_2,unloaded}$ (ml min <sup>-1</sup> )	$\dot{V}_{O_2,max}$ (ml min <sup>-1</sup> )	$\Delta\dot{V}_{O_2}$ (ml min <sup>-1</sup> )
Adult ( <i>n</i> = 9)	39	374 ± 51	566 ± 65	3091 ± 415	2525 ± 335
Elderly ( <i>n</i> = 39)	69	324 ± 14	491 ± 26	1624 ± 83*	1137 ± 69*
E/A × 100	—	87%	87%	52%	45%

Values are means ± s.e.m. Variables:  $\dot{V}_{O_2,rest}$ , resting  $\dot{V}_{O_2}$ ;  $\dot{V}_{O_2,unloaded}$ ,  $\dot{V}_{O_2}$  whilst cycling unloaded;  $\dot{V}_{O_2,max}$ , maximal  $\dot{V}_{O_2}$ ;  $\Delta\dot{V}_{O_2}$ ,  $\dot{V}_{O_2,max} - \dot{V}_{O_2,unloaded}$ ; E/A × 100, elderly/adult value expressed as a percentage. \* Significant difference between the elderly and the adult means.

consisted of 40 subjects (18 male, 22 female; aged 68.8 ± 5.9 years). All subjects voluntarily gave informed, written consent and the study was undertaken in accordance with the Declaration of Helsinki and approved by the University of Washington Human Subjects Review Committee.

#### $\dot{V}_{O_2,max}$ test

**Ergometry procedures.** Subjects completed maximal cycle ergometry (Medgraphics CPE 2000, St Paul, MN, USA) to obtain values for  $\dot{V}_{O_2,max}$  and the corresponding values for leg power output ( $P_{max}$ ), respiratory exchange ratio (RER<sub>max</sub>), and heart rate (HR<sub>max</sub>) at  $\dot{V}_{O_2,max}$ . Twelve elderly subjects were tested on two occasions less than 3 weeks apart and the remaining 28 elderly and the nine adult subjects were tested once. The protocol consisted of a brief familiarization on the cycle and a 1 min pre-exercise period during which resting metabolic data were collected. A 1 min period of unloaded cycling was next and then at minute 2 the ramp increase in workload began at a fixed rate of 10, 12 or 14 W min<sup>-1</sup>. The rate was chosen based on the subject's reported fitness level and body mass. The tests were completed within 7–15 min. Subjects maintained a constant pedalling rate of 60 cycles min<sup>-1</sup>. For the elderly subjects, a physician continuously oversaw a 12 lead electrocardiogram (Quinton 650, Seattle, WA, USA) to monitor heart rate and any cardiac abnormalities during the test. Blood pressure was measured manually every 2 min during the exercise. Criteria for test termination included subject fatigue, signs and symptoms of exercise intolerance, electrocardiogram changes and

abnormal blood pressure or respiratory response in accordance with American College of Sports Medicine guidelines (ACSM, 1991).

**Gas and lactate analysis.** Expired air was analysed using zirconia fuel cell O<sub>2</sub> and CO<sub>2</sub> analysers (Medgraphics). The gas analysers were calibrated with gas mixtures of known O<sub>2</sub> and CO<sub>2</sub> concentrations. The pneumotachograph was adjusted with a calibrated 3 l syringe. Data were averaged over an eight breath period (typically 10–20 s) and reported every 30 s. Blood samples of 1 ml each were drawn from a venous catheter located on the back of a heated hand. Samples were taken as closely as possible to 80% of predicted  $\dot{V}_{O_2,max}$ , at  $\dot{V}_{O_2,max}$ , at 3 min and at 5 min after stopping exercise. Lactate was determined with an automated analyser (Model 1500, Yellow Springs Instruments, Yellow Springs, OH, USA) and the highest level of the last three samples is reported as the maximal level.

**Reproducibility criteria.** The  $\dot{V}_{O_2,max}$  was defined over the last 30 s of the test during which all subjects had a RER<sub>max</sub> > 1.1. The reproducibility of the physiological responses was tested on a subset of 12 elderly subjects who repeated the performance test.  $\dot{V}_{O_2,max}$ , HR<sub>max</sub> and  $P_{max}$  were found not to differ significantly between the two tests with mean values ± s.d. for tests 1 and 2, respectively, as follows:  $\dot{V}_{O_2,max}$ , 22.9 ± 6.5 and 23.8 ± 6.2 ml (kg min)<sup>-1</sup>; HR<sub>max</sub>, 166 ± 10.9 and 163 ± 12.1 beats min<sup>-1</sup>; and  $P_{max}$ , 113 ± 40.7 and 114 ± 39.2 W. There was a significant correlation between tests in  $\dot{V}_{O_2,max}$  ( $r^2 = 0.92$ ), HR<sub>max</sub> ( $r^2 = 0.58$ ), and  $P_{max}$  ( $r^2 = 0.96$ ). For these 12 subjects, the second test was used in our analysis except in two subjects where a clear  $\dot{V}_{O_2}$  plateau was apparent in the first but not in the second test. Blood samples were drawn for analysis of lactate only during the second test.

**Maximal  $\dot{V}_{O_2}$  criteria.** We analysed the ergometer test for all subjects except for the sole case with a mouthpiece leak. Eighty-five percent of the subjects (41/48) met either a  $\dot{V}_{O_2}$  plateau or a blood lactate criterion for maximal  $\dot{V}_{O_2}$ . A plateau or change in  $\dot{V}_{O_2}$  of < 100 ml min<sup>-1</sup> over the last 60 s (Howley *et al.* 1995) was found in 5/9 adult and 29/39 elderly subjects. A lactate level > 8 mM was found in two adult and five elderly subjects not showing a  $\dot{V}_{O_2}$  plateau. The remaining 15% of the subjects who did not achieve the standard  $\dot{V}_{O_2,max}$  criteria nonetheless had an RER<sub>max</sub> > 1.15 and accumulated lactate during the test: [lactate]<sub>max</sub> - [lactate]<sub>rest</sub> ≥ 3.7 mM (no lactate sample in one adult subject). Four of five elderly subjects in this group had a HR<sub>max</sub> at the age-predicted value (i.e. 220 - age), and the final subject not meeting the HR<sub>max</sub> criterion had a final lactate of 7.6 mM.

#### Imaging muscle area and volume

A standard T<sub>1</sub>-weighted magnetic resonance sequence was used to image the thigh and obtain cross-sectional areas (CSA) of the quadriceps, as previously described (Jubrias *et al.* 1997). T<sub>1</sub>-weighted

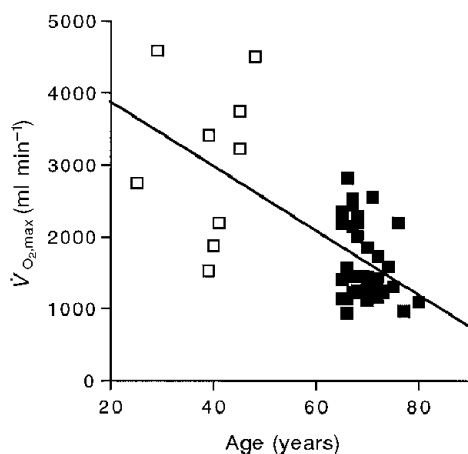


Figure 1. Maximal oxygen uptake rate ( $\dot{V}_{O_2,max}$ ) as a function of age

□, adult subjects; ■, elderly subjects. The regression equation for all subjects is:  $y = -44.1x + 4724.6$ ,  $r^2 = 0.42$ .

Table 2. Quadriceps volume and energetic capacities

Group	$V_Q$ (ml)	Oxidative capacity/ $V_Q$ (mM ATP s <sup>-1</sup> )	Quadriceps oxidative capacity (mmol ATP s <sup>-1</sup> )
Adult ( $n = 9$ )	3560 ± 220	1.16 ± 0.15	4.27 ± 0.75
Elderly ( $n = 39$ )	2370 ± 120*	0.61 ± 0.04*	1.50 ± 0.15*
E/A × 100	67%	53%	36%

Values are means ± s.e.m. Variables:  $V_Q$ , quadriceps volume; E/A × 100 as in Table 1. \* Significant difference between the elderly and the adult means.

images enabled us to distinguish intramuscular fat and omit it from the calculation of contractile tissue area. We determined muscle CSA and volume with standard stereological techniques (Weibel, 1979). Gadeberg *et al.* (1999) provide a detailed error analysis of the Cavalieri method for analysing muscle area from MR images.

**Statistics**

The reproducibility study compared experiments using Student's paired two-tailed *t* test. Group data are reported as means ± s.e.m. and evaluated for differences with Student's unpaired two-tailed *t* test. Standard linear regression methods were used for correlation analysis. Statistical data are reported when a significance level of 0.05 has been reached.

**RESULTS**

Our experimental approach was to measure  $\dot{V}_{O_{2,max}}$  on the cycle ergometer in the adult *vs.* elderly groups. In separate experiments on the same subjects we determined the oxidative capacity of the quadriceps using magnetic resonance methods (Conley *et al.* 2000). These data were used to assess the relationship of the change in muscle properties to the decline in  $\dot{V}_{O_{2,max}}$  with age.

**$\dot{V}_{O_{2,max}}$  test.** Our first question concerns how maximum oxygen uptake rate ( $\dot{V}_{O_{2,max}}$ ) changed with age (Fig. 1). Table 1 shows that the elderly group was significantly below the adult group in  $\dot{V}_{O_{2,max}}$  and in the difference between

unloaded and maximum cycling oxygen uptake rate ( $\Delta\dot{V}_{O_2}$ ). We use the increment in oxygen uptake rate with exercise ( $\Delta\dot{V}_{O_2}$ ) because it eliminates the unloaded cycling  $\dot{V}_{O_2}$  to which the quadriceps makes a minimal contribution. The  $\Delta\dot{V}_{O_2}$  of the elderly group was less than half the value of the adult group. The two groups showed no significant difference in  $\dot{V}_{O_{2,rest}}$  on the cycle or unloaded cycling, resting lactate level (elderly, 1.10 ± 0.05 mM; adult, 0.97 ± 0.12 mM) or peak lactate level (elderly, 7.4 ± 0.4 mM,  $n = 39$ ; adult, 8.3 ± 0.8 mM,  $n = 6$ ).

**Muscle properties.** Our second question concerns how the size and oxidative capacity of the quadriceps differed between our elderly and adult subjects. Table 2 shows that the quadriceps volume ( $V_Q$ ) was significantly lower in the elderly *vs.* adult group. Figure 2 shows a significant decline of  $V_Q$  with age.

The size of the quadriceps relative to the other major muscles involved in cycling was determined from MR images. These images covered enough of the volume of the quadriceps, hamstrings and gluteus to yield the cross-sectional areas (CSA) shown in Fig. 3. The ratio of the quadriceps CSA to the total CSA of the three muscles was significantly smaller in the elderly group (0.44 ± 0.01,  $n = 14$ ) than in the adult group (0.49 ± 0.017,  $n = 6$ ;

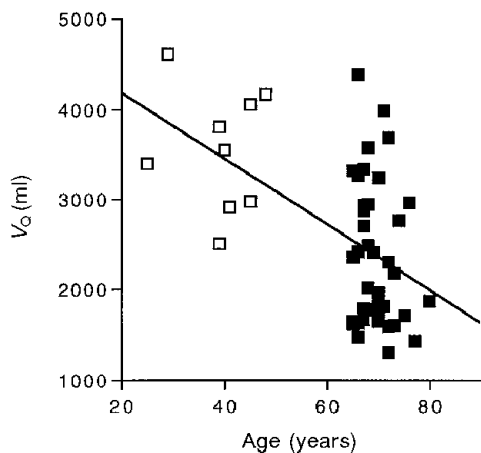


Figure 2. Quadriceps volume ( $V_Q$ ) as a function of age. Symbols as in Fig. 1. The regression equation for all subjects is:  $y = -37.4x + 4973$  ( $r^2 = 0.28$ ).

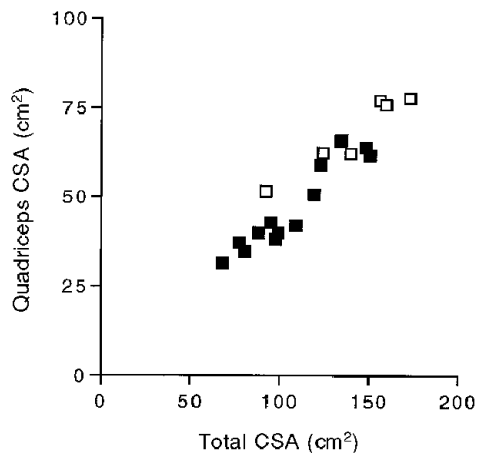


Figure 3. Quadriceps cross-sectional area as a function of the sum of the cross-sectional areas of the quadriceps, gluteus and hamstring muscles. Symbols as in Fig. 1.

$P < 0.025$ ). Thus the quadriceps relative to the other major cycling muscles represents about half the total CSA in the adults, but is a significantly smaller fraction of the total in the elderly.

**Quadriceps oxidative capacity.** Table 2 shows a significant drop in quadriceps volume and oxidative capacity/ $V_Q$  in the elderly compared to the adult group. Also shown is the decline in the product of these two properties which yields the oxidative capacity of the whole quadriceps (hereafter termed quadriceps oxidative capacity). Both muscle properties in the elderly are greater than half the adult value, while the product of the two – the quadriceps oxidative capacity – in the elderly subjects is only 36% of the adult value. This relative decline in quadriceps oxidative capacity is shown in Fig. 4. Removal of the highest point in Fig. 4 did not eliminate the significant difference between the two groups ( $P < 0.0002$ , Student's  $t$  test) or the significant correlation between quadriceps oxidative capacity and age ( $P < 0.0001$ ).

**$\Delta\dot{V}_{O_2}$  vs. muscle properties.** Our final question concerns how the loss of muscle oxidative capacity is related to the decline in  $\dot{V}_{O_{2,max}}$  with age. Figure 5 shows quadriceps oxidative capacity vs.  $\Delta\dot{V}_{O_2}$  for each subject. This figure demonstrates a proportionality of the two variables, although there is a significantly lower quadriceps oxidative capacity/ $\Delta\dot{V}_{O_2}$  in the elderly ( $0.30 \pm 0.02$ ) compared with the adult group ( $0.38 \pm 0.04$ ).

## DISCUSSION

The key result of this study is the correspondence of the decline in quadriceps oxidative capacity to the decline in  $\dot{V}_{O_{2,max}}$  with age. This correspondence was discerned using MR determinations in combination with cycle ergometric measurements of the aerobic limit. These measurements showed that the reductions in muscle size and oxidative capacity/ $V_Q$  together – rather than any single property – resulted in a decline in quadriceps oxidative capacity

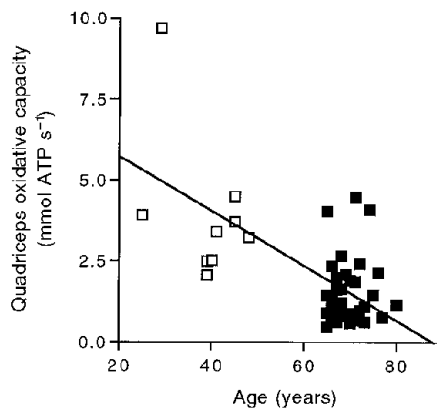


Figure 4. Quadriceps oxidative capacity as a function of age

Symbols are as in Fig. 1. The regression equation for all subjects is:  $y = -0.086x + 7.498$  ( $r^2 = 0.44$ ).

proportional to the loss of  $\dot{V}_{O_{2,max}}$  between the adult and elderly groups.

This comparison of quadriceps properties and  $\dot{V}_{O_{2,max}}$  depends on several assumptions: (1) that the metabolic response measured by MR is reflected in the pulmonary oxygen uptake underlying our  $\dot{V}_{O_{2,max}}$  determination, (2) that electrical stimulation and the  $\dot{V}_{O_{2,max}}$  test fully recruit the fibres of the quadriceps, and (3) that the MR determinations reasonably estimate the quadriceps oxidative capacity.

**PCr dynamics and pulmonary  $\dot{V}_{O_2}$ .** The dynamics of PCr generates the signals activating mitochondrial oxygen uptake (see Meyer, 1988; Conley *et al.* 2000). Several studies have shown a close association between these physiological responses of muscle and the whole body pulmonary oxygen uptake. Simultaneous measurements of the PCr dynamics in the quadriceps and pulmonary  $\dot{V}_{O_2}$  show the same kinetics (Rossiter *et al.* 1999). A similar correspondence has been found in separate MR and  $\dot{V}_{O_2}$  measurements in the plantar flexors (McCreary *et al.* 1996) and in the PCr dynamics after plantar flexor exercise vs. the  $\dot{V}_{O_2}$  kinetics in cycling (Barstow *et al.* 1994). These studies confirm that the change in pulmonary  $\dot{V}_{O_2}$  with exercise reflects an increase in muscle  $\dot{V}_{O_2}$  resulting from changes in PCr level.

**Fibre recruitment in the MR and  $\dot{V}_{O_{2,max}}$  determinations.** All of the fibres of the quadriceps appear to be activated in both the measurements of oxidative capacity by MR and the  $\dot{V}_{O_{2,max}}$  test on the ergometer. Full recruitment of the quadriceps during cycling at levels close to  $\dot{V}_{O_{2,max}}$  is indicated by glycogen depletion measurements (see Saltin & Gollnick, 1983) and by the increase in mitochondrial volume density ( $V_v(mt,f)$ ) in all fibre types after endurance training (Howald *et al.* 1985). Complete recruitment of the quadriceps in the MR determination is attained by electrical stimulation at an intensity that evokes a maximal EMG response (Blei *et al.* 1993). Full recruitment

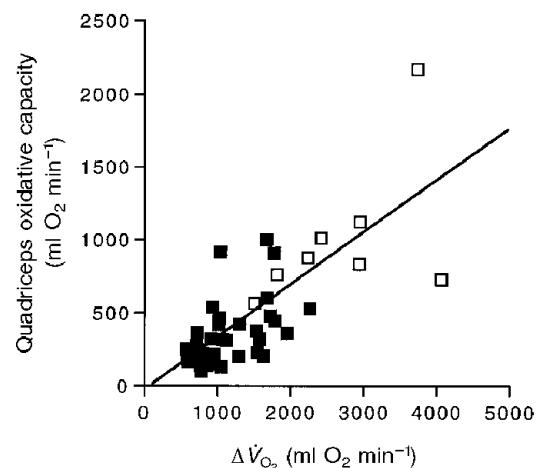


Figure 5. Quadriceps oxidative capacity as a function of the increment in oxygen consumption between unloaded cycling and  $\dot{V}_{O_{2,max}}$  ( $\Delta\dot{V}_{O_2}$ )

Symbols are as in Fig. 1. The regression equation for all subjects is:  $y = 0.36x - 46.97$  ( $r^2 = 0.57$ ).

of the fibres of the quadriceps group in both determinations permit us to compare the MR and  $\dot{V}_{O_{2,max}}$  test results.

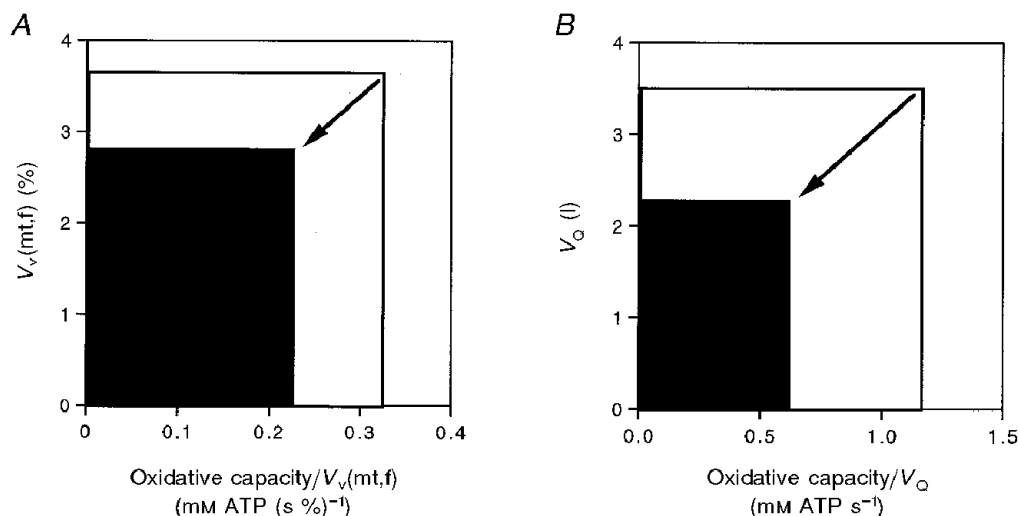
**MR determination of quadriceps oxidative capacity.** The PCr recovery time course following exercise is an index of the oxidative properties of muscle (McCully *et al.* 1993; Paganini *et al.* 1997). The resting PCr level along with the PCr dynamics provide the information necessary to estimate oxidative capacity in the muscle. We found this estimate to correspond with the oxidative capacity estimated from  $V_v(mt,f)$  of the quadriceps in adults (Conley *et al.* 2000). The quadriceps appears to work at its oxidative capacity during cycling at  $\dot{V}_{O_{2,max}}$  since the PCr level drops to near zero and no increase in  $\dot{V}_{O_2}$  is possible with increases in work (Richardson *et al.* 1995). In addition, Hoppeler *et al.* (1985) found that the increase in oxygen consumption predicted from the rise in  $V_v(mt,f)$  in quadriceps muscle accounted for the elevation in  $\dot{V}_{O_{2,max}}$  after cycle endurance training in young subjects. Thus direct measurement of quadriceps oxygen uptake and the changes in mitochondrial properties with training indicate that the quadriceps operates at its oxidative capacity during cycling at  $\dot{V}_{O_{2,max}}$  in adult muscle. We can now ask how the changes in quadriceps properties relate to the decline in  $\dot{V}_{O_{2,max}}$  with age.

**Decline in aerobic performance and muscle properties with age.** The well-established decline in  $\dot{V}_{O_{2,max}}$  with age is shown in Fig. 1, and the resulting drop in the increment in  $\dot{V}_{O_2}$  between unloaded cycling and maximal uptake rate ( $\Delta\dot{V}_{O_2}$ ) appears in Table 1. Babcock *et al.* (1994) reported that the  $\dot{V}_{O_2}$  time course from rest to submaximal exercise is slowed as a function of age. A slowing of PCr recovery after exercise with age has also been reported (McCully *et al.* 1993; Conley *et al.* 2000). These time course changes indicate that a decline in whole body and muscle oxidative properties in part underlies the reduction in  $\dot{V}_{O_{2,max}}$  with age.

This decline in muscle oxidative properties is accompanied by a well documented (see Jubrias *et al.* 1997) drop in muscle volume ( $V_Q$ , Fig. 2). Unique to this study is our finding that the product of  $V_Q$  (Fig. 2) and oxidative capacity/ $V_Q$  (Conley *et al.* 2000) – quadriceps oxidative capacity – also drops as a function of age (Fig. 4). Table 2 shows that the quadriceps oxidative capacity dropped in the elderly relatively more than either muscle property alone and was a slightly smaller percentage of the adult value (36%) than was  $\Delta\dot{V}_{O_2}$  (45%).

These results emphasize the importance of measuring both muscle volume and oxidative properties in studying the link between muscle properties and  $\dot{V}_{O_{2,max}}$ . Many muscles show a smaller change in their oxidative properties with age than does  $\dot{V}_{O_{2,max}}$  (see Houmard *et al.* 1998). This study demonstrates that both  $V_Q$  and oxidative capacity/ $V_Q$  decline less with age than does  $\dot{V}_{O_{2,max}}$  (Tables 1 and 2). However, a key point of this study is that the size of the muscle along with the volume-specific oxidative properties are important determinants of the capacity for oxygen uptake. Thus an individual can have the same quadriceps oxidative capacity with a large  $V_Q$  and low oxidative capacity/ $V_Q$  and vice versa. This point is illustrated by the considerable individual variation (low correlation) of either  $V_Q$  ( $r^2 = 0.28$ ; Fig. 2) or oxidative capacity/ $V_Q$  ( $r^2 = 0.34$ ; Conley *et al.* 2000) alone with age, but a higher correlation of the product of the two, quadriceps oxidative capacity ( $r^2 = 0.44$ ; Fig. 4), with age and with  $\dot{V}_{O_{2,max}}$  ( $r^2 = 0.57$ ; Fig. 5).

**Does the loss of  $\Delta\dot{V}_{O_2}$  reflect the decline in muscle properties with age?** Figure 5 shows that quadriceps oxidative capacity varies linearly with  $\Delta\dot{V}_{O_2}$ . The slope of this plot indicates that the quadriceps are responsible for on average 0.36 of the increment in oxygen uptake above low load cycling. An independent estimate of the oxygen



**Figure 6.** Change in muscle properties between adult (□) and elderly (■) groups

*A*, decline in volume-specific oxidative capacity as the product of the loss of mitochondrial volume density ( $V_v(mt,f)$ ) and of mitochondrial capacity (oxidative capacity/ $V_v(mt,f)$ ). *B*, decline in whole muscle oxidative capacity as the product of loss of muscle volume ( $V_Q$ ) and volume-specific oxidative capacity (oxidative capacity/ $V_Q$ ).

uptake of the quadriceps at  $\dot{V}_{O_2, \max}$  comes from the work accomplished by this muscle group along with the percentage contribution of the legs to the total  $\dot{V}_{O_2, \max}$ . The quadriceps generate 0.35 of the total work by the legs during cycling at the pedalling rate (60 r.p.m.) and the range of leg power outputs found in this study (120–240 W; Ericson, 1988). With the legs consuming 0.85 of the oxygen used during cycling at  $\dot{V}_{O_2, \max}$  (Harms *et al.* 1997), 0.35 of the leg work production yields a 0.30 contribution (i.e.  $0.35 \times 0.85 = 0.3$ ) of quadriceps oxygen uptake to  $\dot{V}_{O_2, \max}$ . These calculations confirm our estimate of the quadriceps quantitative contribution to  $\Delta\dot{V}_{O_2}$  and the important role that the loss of quadriceps oxidative capacity has in the decline in  $\dot{V}_{O_2, \max}$  with age.

**Central vs. peripheral limitations to  $\dot{V}_{O_2, \max}$ .** The slightly larger loss of quadriceps oxidative capacity compared with  $\Delta\dot{V}_{O_2}$  between the two groups argues against a significant central cardiovascular limitation to  $\dot{V}_{O_2, \max}$ . Proctor & Joyner (1997) suggested that the significantly reduced  $\dot{V}_{O_2, \max}$  per appendicular muscle mass in trained elderly compared with trained young was due to lower maximal  $O_2$  delivery. Evidence for an  $O_2$  delivery limitation to  $\dot{V}_{O_2, \max}$  has been reported for young, trained subjects (Richardson *et al.* 1999). However, two recent studies demonstrated that blood flow and oxygen delivery were not limiting to  $\dot{V}_{O_2, \max}$  in either trained (Pedersen *et al.* 1999) or untrained (Cardus *et al.* 1998) young subjects. Both studies that failed to find an  $O_2$  delivery limitation suggested a muscle mitochondrial limitation to  $\dot{V}_{O_2, \max}$  in these subjects. Thus cardiovascular limitations may be restricted to highly trained subjects and may not be present in the general population.

Our data are from recreationally active elderly and show a smaller relative quadriceps oxidative capacity (36%) than  $\dot{V}_{O_2, \max}$  (52%) or  $\Delta\dot{V}_{O_2}$  (45%) compared to adults. This greater decline in peripheral oxidative capacity than of whole body oxygen consumption may reflect a larger decline in the properties of the quadriceps relative to other muscles involved in cycling. Reimers *et al.* (1998) found that age-related atrophy does not affect all muscles equally. A greater atrophy of the quadriceps relative to other muscles is evident in the smaller fraction of this muscle group of the total CSA of the cycling muscles in the elderly (0.44) compared with adults (0.49). Confirming the differential ageing effects on muscle groups is the Chilibeck *et al.* (1996) finding of a significant decline in  $\dot{V}_{O_2}$  kinetics during cycling but not during plantar flexion in the elderly. They suggested that this difference reflects a smaller chronic use of the quadriceps than the plantar flexors during walking. We found that the age-related change in quadriceps muscle properties resulted in greater loss of quadriceps oxidative capacity than  $\Delta\dot{V}_{O_2}$ . A greater loss of muscle *vs.* whole body capacity is opposite to the expectation of an increased cardiovascular limitation to  $\dot{V}_{O_2, \max}$  with age. This result points to the important role of skeletal muscle oxidative capacity in the loss of whole body maximal oxygen uptake with age.

## Conclusions

Figure 6 summarizes the key cellular and muscle factors contributing to the decline in  $\dot{V}_{O_2, \max}$  with age. First, we have reported that the oxidative capacity per quadriceps volume declined because of losses of both mitochondrial content and function (oxidative capacity per  $V_v(\text{mt}, \text{f})$ ; Conley *et al.* 2000). Figure 6A shows that similar relative declines in oxidative capacity per  $V_v(\text{mt}, \text{f})$  and  $V_v(\text{mt}, \text{f})$  itself are responsible for this loss in oxidative capacity/ $V_Q$ , as shown by the decrease in the size of the box. A second major change was the volume of quadriceps muscle. Figure 6B shows that the loss of oxidative capacity/ $V_Q$  and of  $V_Q$  contributed nearly equally to the reduction of quadriceps oxidative capacity with age. The result of these muscle changes is a relative decline in the quadriceps oxidative capacity close to that found for  $\dot{V}_{O_2, \max}$  between age groups. The significant contribution of the quadriceps oxidative capacity to  $\dot{V}_{O_2, \max}$  indicates that the reductions in muscle properties in the elderly are important determinants of the age-related reduction in  $\Delta\dot{V}_{O_2}$  and  $\dot{V}_{O_2, \max}$  found in this study.

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