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Determinants of $VO_{2\,max}$ decline with aging: an integrated perspective

Andrew C. Betik and Russell T. Hepple

Abstract: Aging is associated with a progressive decline in the capacity for physical activity. Central to this decline is a reduction in the maximal rate of oxygen utilization, or $VO_{2\,max}$. This critical perspective examines the roles played by the factors that determine the rate of muscle oxygen delivery versus those that determine the utilization of oxygen by muscle as a means of probing the reasons for $VO_{2\,max}$ decline with aging. Reductions in muscle oxygen delivery, principally due to reduced cardiac output and perhaps also a maldistribution of cardiac output, appear to play the dominant role up until late middle age. On the other hand, there is a decline in skeletal muscle oxidative capacity with aging, due in part to mitochondrial dysfunction, which appears to play a particularly important role in extreme old age (senescence) where skeletal muscle $VO_{2\,max}$ is observed to decline by approximately 50% even under conditions of similar oxygen delivery as young adult muscle. It is noteworthy that at least the structural aspects of the capillary bed do not appear to be reduced in a manner that would compromise the capacity for muscle oxygen diffusion even in senescence.

Key words: aging, maximal oxygen consumption, oxygen delivery, capillaries, mitochondria.

Résumé : Le vieillissement s'accompagne d'une diminution graduelle de la capacité d'effort physique. La variable principalement touchée est le taux maximal d'utilisation de l'oxygène, soit le $VO_{2\,max}$. Dans cet article, nous analysons le rôle respectif joué par les facteurs du transport de l'oxygène vers les muscles et par ceux du système d'extraction d'oxygène effectué par les muscles afin d'identifier les facteurs responsables de la diminution du $VO_{2\,max}$ dans le processus du vieillissement. La diminution du transport de l'oxygène vers les muscles, causée principalement par la diminution du débit cardiaque et probablement aussi par une mauvaise distribution du débit cardiaque, semble jouer le rôle principal jusque vers la fin de l'âge mûr. D'autre part, on observe une diminution de la capacité oxydative du muscle squelettique avec l'âge ; ce phénomène est attribuable en partie à des anomalies dans la mitochondrie qui semble jouer un rôle particulièrement important à un âge très avancé ; à cet âge, le $VO_{2\,max}$ des muscles squelettiques est d'environ 50 % de la valeur observée chez un jeune adulte dans les mêmes conditions de fourniture d'oxygène. Notons cependant que les caractéristiques structurelles du lit capillaire ne semble pas modifiées de manière à compromettre la capacité de diffusion de l'oxygène même à un âge très avancé.

Mots-clés : vieillissement, consommation maximale d'oxygène, transport de l'oxygène, capillaires, mitochondrie.

[Traduit par la Rédaction]

Introduction

Since the pioneering studies of Hill et al. (1924), physiologists have been fascinated with the quest to understand what limits our maximal ability to utilize oxygen during exercise ($VO_{2\,max}$). Whereas for most healthy individuals $VO_{2\,max}$ has little bearing on everyday life, and thus, the issue of what limits $VO_{2\,max}$ is arguably of lesser practical concern, the age-related decline in $VO_{2\,max}$ is such that the ability of elderly individuals to perform everyday tasks becomes greatly dependent upon $VO_{2\,max}$ (Paterson et al. 2004). For this reason, understanding the physiological basis for the decline in $VO_{2\,max}$ with aging has clear practical significance in terms of identifying means by which the capacity for an independent lifestyle can be maintained. On the basis that $VO_{2\,max}$ is determined by both the capacity for oxygen delivery and for oxygen utilization (Di Prampero 1985; Lindstedt et al. 1988; Wagner 1995) (Fig. 1), and because the majority of the O_2 consumed at $VO_{2\,max}$ is within the contracting locomotor muscles (Knight et al. 1992), the focus of this critical review will be on understanding how aging impacts the factors determining the capacity for oxygen delivery and oxygen utilization at the level of skeletal muscle.

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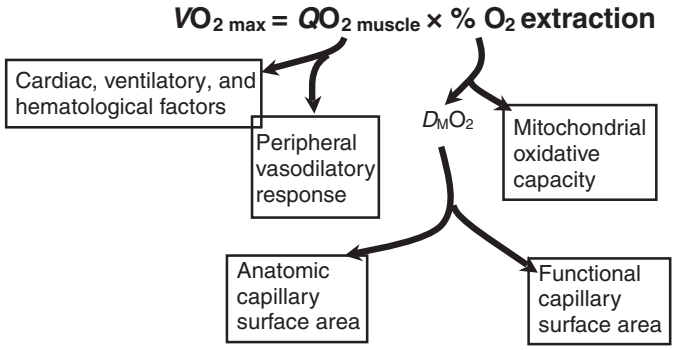
Fig. 1. Determinants of $VO_{2\,max}$. QO_2, convective oxygen delivery (product of cardiac output and arterial oxygen content); D_MO_2, muscle oxygen diffusing capacity.



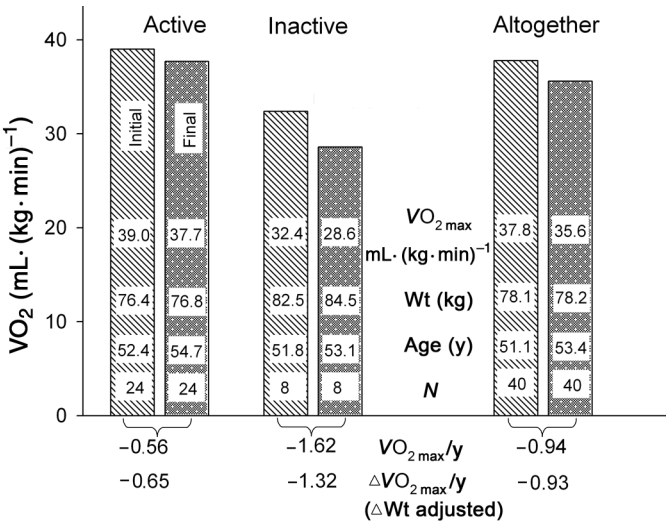
Changes in $VO_{2\,max}$ with aging

One of the first studies to report an age-related decline in $VO_{2\,max}$ was by Dehn and Bruce (1972). Specifically, they followed a group of 40 healthy older men across a 2.3 year period and compared the degree of $VO_{2\,max}$ decline between subjects who remained physically active versus those who were sedentary across the same time interval, finding that being physically active could slow but not prevent the age-related decline in $VO_{2\,max}$ seen in sedentary subjects (Fig. 2). Since that time, both cross-sectional and longitudinal studies have reached similar conclusions and show that the rate of decline in sedentary individuals is approximately 10% per decade (Inbar et al. 1994; Stathokostas et al. 2004; Toth et al. 1994), and about 5% per decade in highly active individuals (Kasch et al. 1999; Pollock et al. 1997; Trappe et al. 1996; Wiswell et al. 2001). Interestingly, a recent study by Stathokostas et al. (2004) noted that taking changes in physical activity levels into account explained only a trivial fraction of the longitudinal decline in $VO_{2\,max}$ observed over a 10 year follow-up period in older men and women, underscoring that there is a significant component of $VO_{2\,max}$ decline with aging that is not simply due to lower physical activity levels. Although the majority of the literature treats the decline in $VO_{2\,max}$ with aging as being linear, a recent study examining 810 healthy men and women over 8 years observed that, whereas $VO_{2\,max}$ declined at a rate of approximately 3%–6% per decade in the 20s and 30s, this accelerated to more than 20% per decade at ages of 70 years and older (Fleg et al. 2005). Consistent with this point, another recent study of age-related declines in $VO_{2\,max}$ during treadmill running in rats demonstrated a markedly more dramatic decline between late middle age (24 months) and senescence (36 months) than between young adulthood (12 months) and late middle age (Olfert et al. 2004). This non-linearity of changes in aerobic performance is often difficult to assess in the literature, as only two time points or ages are often studied. This is also important in considering the causes of the decline in $VO_{2\,max}$ with aging, since different processes may be relevant at later ages, as will be discussed in the sections that follow.

Convective oxygen delivery

A wealth of studies has demonstrated the effects of altering convective oxygen delivery on $VO_{2\,max}$ in young adults. Interestingly, elevating oxygen delivery beyond that normally seen (e.g., by inhaling a hyperoxic gas mixture) has less benefit for young sedentary individuals than exercise-trained individuals (Roca et al. 1992; Wagner et al. 1998), a fact that could be relevant to aged subjects, since a decline in physical activity is a well known occurrence with aging. However, putting this aside, aging affects many factors that can negatively affect blood flow, such as reduced maximal cardiac output (McElvaney et al. 1989) and reduced vascular conductance (Lawrenson et al. 2003; Proctor et al. 1998*a*). This latter factor is likely related to a decreased endothelial-derived vasoreactivity (Muller-Delp et al. 2002*b*; Taddei et al. 1995) and altered myogenic responsiveness (Muller-Delp et al. 2002*a*) with aging. An important question here concerns whether a decline in muscle blood flow during exercise causes the decline in $VO_{2\,max}$, or whether it is reduced secondary to reduced muscle metabolic demand. Comparisons of small versus large muscle group exercise, which alters the metabolic demand, helps to identify inadequacies of blood flow. As the following sections will illustrate, small muscle group exercise may not have a blood flow limitation, but during large muscle group and whole-body exercise,

Fig. 2. Effect of physical activity on age-related decline of $VO_{2\,max}$ across a 2.3 year period in active vs. inactive subjects. Values printed in the bars represent (from top to bottom) $VO_{2\,max}$ ($mL \cdot min^{-1} \cdot kg^{-1}$), body mass (kg), age (y) and number of subjects. Reproduced with permission from Dehn and Bruce. J. Appl. Physiol. **33**(6): 805–807. ©1972 The American Physiological Society.

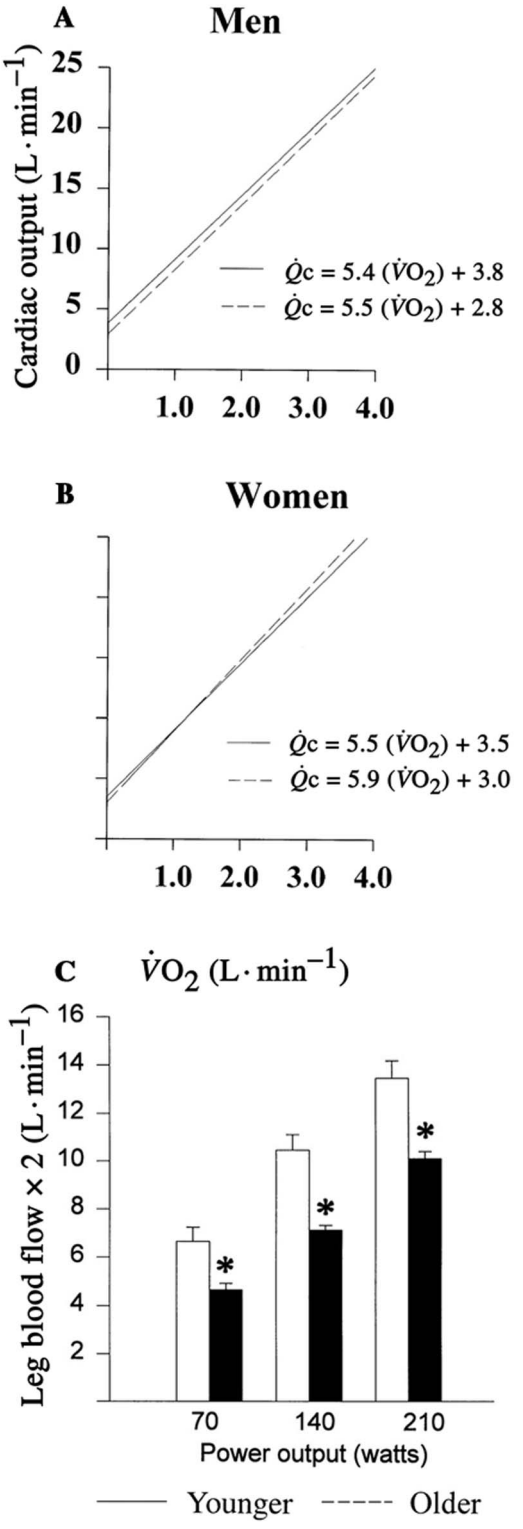


muscle blood flow and thus O_2 delivery is lower, likely contributing to the reduced $VO_{2\,max}$ with aging.

The first report stating that aging reduces muscle blood flow during whole-body (submaximal) exercise was made by Wahren and colleagues in what were described as healthy, well-trained, 52- to 59-year-old men (Wahren et al. 1974). More recent studies in sedentary older men (Beere et al. 1999; Poole et al. 2003) and women (Proctor et al. 2004) have similar findings. In seeking to explain the lower muscle blood flow, the reduced maximal cardiac output during exercise seen with aging is an obvious starting point (Faulkner et al. 1977; Hagberg et al. 1985; McElvaney et al. 1989; Ogawa et al. 1992). However, investigators have also considered whether an altered distribution of that cardiac output might be playing an important role. In support of the idea that a smaller fraction of the cardiac output is directed towards active limb muscle with aging, Proctor and colleagues showed that although the cardiac output response to a given level of submaximal exercise was preserved in endurance-trained older adults (64 years) versus their younger counterparts (Fig. 3, top panel) (Proctor et al. 1998*b*), the blood flow going to the legs during submaximal cycling exercise was 20%–30% lower in the aged subjects (Proctor et al. 1998*a*), suggesting an impaired distribution of cardiac output with aging (Fig. 3, bottom panel). It should be noted that VO_2 was not different between age groups for 3 different power outputs, so for ease of comparing these figures, VO_2 and power output can be considered interchangeable. In summary, this figure adapted from their paper shows that age does not alter the cardiac output – O_2 uptake relationship; however, for a given power output (and cardiac output), aged subjects have significantly lower leg blood flow. Poole and colleagues later observed a very similar response in extremely sedentary older (70 years) subjects, particularly at higher exercise intensities (Poole et al. 2003). However, recently another study from Proctor's group, this time examining what were termed "normally active" subjects (i.e., they exhibited a level of physical activity that was similar to others their age, being more active than sedentary), observed no difference in leg muscle blood flow during submaximal exercise in the older subjects (66 years) (Proctor et al. 2003). It is noteworthy that the disparate findings between these three studies are not easily explained by the differences in physical activity habits of the subjects, since maldistributed cardiac output was found in older trained and very sedentary subjects, but not in subjects who exhibited intermediate or what was termed "normal" levels of physical activity for their age, leaving uncertainty about the potential for maldistribution of cardiac output to contribute to an age-related decline in muscle blood flow at $VO_{2\,max}$. Furthermore, there are no data concerning these responses in senescent individuals (i.e., at ages corresponding to ≥50% mortality), which is a time that is associated with accelerated aging-related physiological decline and accelerated loss of $VO_{2\,max}$ (Fleg et al. 2005; Olfert et al. 2004). Further studies are clearly required to resolve this issue.

A landmark study in which the same subjects were tested after a 30 year period observed no change in maximal cardiac output at middle age (50 years) compared with when they were younger (20 years), and that the decline in $VO_{2\,max}$ was attributed to a decline in oxygen extraction (McGuire et

Fig. 3. Cardiac output versus oxygen consumption (A–B) and leg blood flow versus power output (C) in endurance-trained young adult (open bars) versus older (filled bars) human subjects. Reproduced with permission from Proctor et al. J. Appl. Physiol. **84**(2): 599–605 (A–B) and Proctor et al. J. Appl. Physiol. **85**(1): 68–75 (C). ©1998 The American Physiological Society.



al. 2001*a*). When these same subjects underwent a 6 week training program, again there was no change in maximal cardiac output, and the 16% improvement in $\dot{V}O_{2\,max}$ was accounted for entirely by an increase in arterial–venous O_2 difference, suggesting that the adaptations facilitating the improvement in $\dot{V}O_{2\,max}$ were peripheral to the heart (McGuire et al. 2001*b*). The significance of these findings is that they underscore the importance of factors peripheral to cardiac output as contributors to the age-related decline in $\dot{V}O_{2\,max}$.

Two additional studies provide further evidence for reduced muscle blood flow causing a reduction in $\dot{V}O_2$. Lawrenson and colleagues compared the metabolic responses during cycling versus single-leg knee-extensor exercise. Firstly, they showed that late middle-aged subjects (67 years) had a lower quadriceps muscle blood flow for the same work rate and muscle mass throughout a graded maximal knee-extensor test. Secondly, the difference in $\dot{V}O_{2\,max}$ between young and late middle-aged subjects was much greater during cycling exercise (~35%) compared with during knee- extensor exercise (~20%, not significant) (Lawrenson et al. 2003), supporting the idea that reductions in muscle blood flow during exercise with aging can contribute to the reduction in $\dot{V}O_{2\,max}$. Also supporting this point, Scheuermann and colleagues showed that the $\dot{V}O_2$ kinetics response to moderate exercise was greatly accelerated when muscle blood flow was increased by a preceding bout of exercise in late middle-aged (65 years), but not young, adult subjects (Scheuermann et al. 2002). In regard to this latter study, it is also relevant that even with the acceleration of $\dot{V}O_2$ kinetics following a priming bout of high-intensity exercise in the aged subjects, their response was still slower than that of the young adult subjects (Scheuermann et al. 2002), suggesting some residual limitation may remain within the contracting muscles. This same group strengthened this finding a few years later using near-infrared spectroscopy to differentiate the balance between O_2 delivery and O_2 utilization (DeLorey et al. 2004). Using the same protocol, compared with the young adults, the late middle-aged subjects experienced a faster $\dot{V}O_2$ response and slower adaptation of deoxyhemoglobin after a previous bout of heavy exercise, suggesting that O_2 delivery is responsible for the faster O_2 kinetics. In summary, these results indicate that during normal exercise conditions (without a previous exercise bout), older humans have lower O_2 delivery that limits the rate at which the muscles increase O_2 consumption in the non-steady state.

Turning to the animal literature, there is evidence of a reduced muscle blood flow during high-intensity muscle contractions (Irion et al. 1987) and, more recently, Musch and colleagues observed a marked alteration in blood flow distribution between oxidative and glycolytic muscle regions (Musch et al. 2004). In this latter study, young adult and late middle-aged rats were run on a treadmill at the same speed and elevation, and microspheres were injected once the animals reached steady state. Interestingly, although total leg blood flow was similar between the ages, individual muscle analyses showed that whereas glycolytic muscle regions were receiving more blood flow with aging, the oxidative muscle regions were receiving less blood flow with aging (Musch et al. 2004) (Fig. 4). Although the relatively higher exercise intensity for the aged rats might be considered a confounding factor (since this would evoke a greater metabolic perturbation, particularly in the glycolytic muscles), the results are nonetheless compelling and suggest that it might be premature to discount that a maldistributed cardiac output could contribute to impaired muscle blood flow, and thus oxygen delivery, at $\dot{V}O_{2\,max}$ with aging.

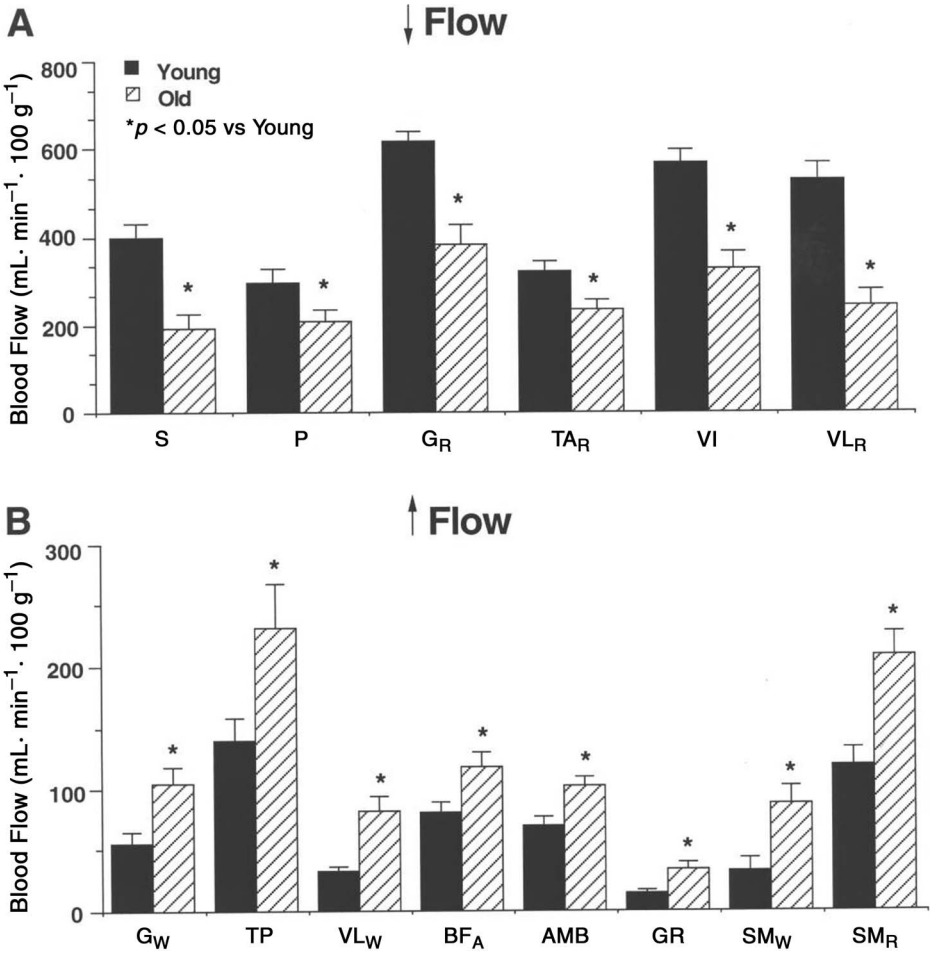
It is important to note that a reduction in muscle blood flow during exercise is not universally seen with aging. Jasperse et al. (1994) studied forearm blood flow following handgrip exercise and showed no impairment in 60- to 74-year-old subjects. Similarly, Magnusson et al. (1994) observed no decline in maximal leg perfusion during knee-extensor exercise in 44- to 69-year-old subjects who had well-preserved skeletal muscle mass, although it should be noted that in this latter study the older subjects had a greater sympathetic drive (e.g., vascular conductance was reduced), which is similar to observations in other studies (Poole et al. 2003; Proctor et al. 1998*a*). These studies that do not show a reduced muscle blood flow involve relatively smaller muscle groups (handgrip exercise or knee-extension exercise), which suggests that blood flow limitation may only become apparent when larger and (or) more muscle groups are involved. Thus, collectively, the data support the idea that restrictions in blood flow, occurring secondary to altered cardiac output distribution and (or) reduced maximal cardiac output, contribute to reduce $\dot{V}O_{2\,max}$ during whole-body exercise with aging, although as noted above, no study to date has considered these responses in senescence.

Diffusive oxygen delivery

The idea that the diffusion of oxygen from blood to muscle-fiber mitochondria plays an important role in determining $\dot{V}O_{2\,max}$ is generally supported by the literature (Hepple et al. 1997; Mathieu-Costello et al. 1992; Mole et al. 1999; Richardson et al. 1995; Wagner 1995), although unambiguous direct evidence remains to be provided. This caveat aside, it is thought that capillary surface area (Mathieu-Costello 1993), particularly the aggregate surface area of capillaries that is adjacent to red cells (Federspiel and Popel 1986), plays an important role in determining the diffusion of oxygen from red cell to fiber mitochondria in contracting muscles. From a structural perspective, capillary surface area within a muscle is determined by the number of capillaries around a fiber, the capillary sharing factor, and fiber size (smaller fibers permitting more capillaries to be packed into a given area). From a functional perspective, the aggregate surface area of capillaries that is adjacent to red cells is determined by the number of perfused capillaries and the capillary hematocrit (Kindig et al. 2002; Poole et al. 1997). Thus, there are several considerations when evaluating the potential for alterations in the so-called muscle-diffusing capacity to contribute to declining $\dot{V}O_{2\,max}$ with aging.

In rats, the number of capillaries around a fiber does not decline with aging in slow or fast muscles even to senescence (Mathieu-Costello et al. 2005). In late middle age, a tendency toward elevated fiber size in postural muscles (e.g., soleus muscle) and a reduction in fiber size in glycolytic muscle (e.g., white region of the gastrocnemius

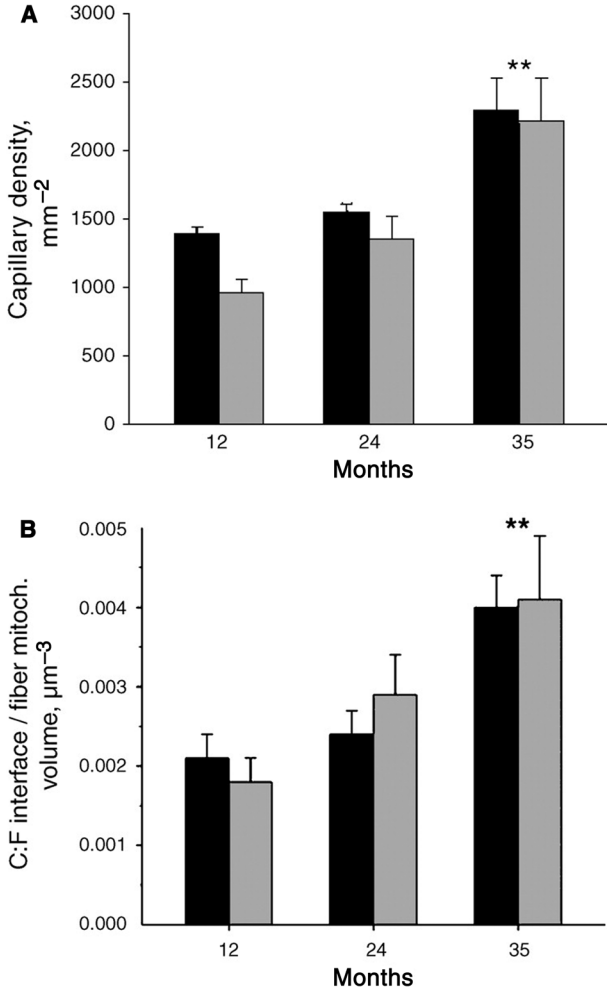
Fig. 4. Blood flow in glycolytic (top panel) and oxidative (bottom panel) muscles of young adult (black bars) versus late middle-aged (cross-hatched bars) Fischer 344 × Brown Norway F_1 hybrid rats during a bout of submaximal treadmill running. S, soleus; P, plantaris; G_R, red portion of gastrocnemius; TA_R, red portion of tibialis anterior; VI, vastus intermedius; VL_R, red portion of vastus lateralis; G_w, white portion of gastrocnemius; TP, tibialis posterior; VL_W, white portion of vastus lateralis; BF_A, anterior portion of biceps femoris; AMB, adductor magnus and brevis; GR, gracilis; SM_W, white portion of semimembranosus; SM_R, red portion of semimembranosus. Reproduced with permission from Musch et al. J. Appl. Physiol. **96**: 81–88. ©2004 The American Physiological Society.



muscle) leads to a decrease and an increase, respectively, in capillary density (i.e., the number of capillaries per cross-sectional area of muscle) (Hepple and Vogell 2004). However, by senescence even the soleus muscle exhibits an increase in capillary density consequent to severe fiber atrophy (Mathieu-Costello et al. 2005) (Fig. 5, top panel). It should be noted that the number of capillaries around a fiber has been observed to decrease in humans, but this appears to be only for type II fibers and after accounting for fiber atrophy there is little to no difference in capillary density with age (Coggan et al. 1992*a*; Croley et al. 2005; Ryan et al. 2006). Therefore, both human and rodent studies suggest that any alterations in capillarization with aging are unlikely to have an adverse impact on the structural capacity for oxygen diffusion from blood to myocyte mitochondria, and thus are unlikely to play a major role in the age-related decline of $VO_{2\,max}$. It should also be noted that rodent studies indicate that, irrespective of any changes in capillary density with aging, when expressed in relation to either the fiber mitochondrial oxidative capacity (Hepple and Vogell 2004) or mitochondrial volume (Mathieu-Costello et al. 2005), the capillarization is actually excessive relative to the fiber oxygen demand in aged muscles (Fig. 5, bottom panel), suggesting a surfeit in the structural surface area available for oxygen delivery to fiber mitochondria with aging in rodents. No corresponding data for aged humans are available at this time.

To date, there are no published data concerning the behaviour of the erythrocytes within the aged microvasculature in response to muscle contractions. However, a recent study showed that there was a faster erythrocyte velocity in resting spinotrapezius muscle of late middle-aged rats, which if also true during muscle contractions could limit the time available for oxygen off-loading from hemoglobin in the microcirculation, thereby impairing muscle oxygen delivery (Russell et al. 2003). Clearly, further work on this important topic, not only in the context of contracting muscle but also extending studies into the senescent period, would be useful in evaluating the potential for alterations in the functional properties of the microcirculation to affect $VO_{2\,max}$ with aging.

Fig. 5. Capillary density (top panel) and capillary surface per unit of fiber mitochondrial volume (bottom panel) in soleus muscle (black bars) and extensor digitorum longus muscle (grey bars) of young adult (12 months), late middle-aged (24 months), and senescent (35 months) Fischer 344 × Brown Norway F_1 hybrid rats. Reproduced with permission from Mathieu-Costello et al. J. Appl. Physiol. **99**: 281–289. ©2005 The American Physiological Society.



Mitochondria and oxygen utilization

As noted previously (see section "Convective oxygen delivery"), at least one prior study indicated the potential for alterations within the skeletal muscles to contribute to a decline in $\dot{V}O_{2\,max}$ with aging. Specifically, the fact that the $\dot{V}O_2$ kinetics response to moderate exercise remained slower in aged subjects even after a priming exercise bout had minimized the limitation imposed by a sluggish oxygen delivery response (Scheuermann et al. 2002) points towards limitations within the skeletal muscles. Also, microcirculatory structure (and perhaps also function) appears to be more than adequate (Hepple and Vogell 2004) even into senescence (Mathieu-Costello et al. 2005; (see section "Diffusive oxygen delivery", this paper). Thus, if one were to observe a decline in $\dot{V}O_{2\,max}$ with aging despite matching muscle convective oxygen delivery, this would strongly implicate a limitation within the contracting muscles themselves. To tackle this question directly, we utilized a pump-perfused rat hindlimb model to permit us to consider the $\dot{V}O_{2\,max}$ response in electrically stimulated skeletal muscles of young adult and aged rats at matched rates of muscle convective oxygen delivery (Hagen et al. 2004). As shown in Fig. 6, we observed that despite matching muscle convective oxygen delivery across age groups, there was a modest reduction in $\dot{V}O_{2\,max}$ in late middle age and a profound decrease in senescence. Furthermore, this decline in $\dot{V}O_{2\,max}$ under these pump-perfused conditions was proportional to an age-related decline in some indices of skeletal muscle oxidative capacity (Hagen et al. 2004). On balance, these results suggest that an age-related reduction in mitochondrial oxidative capacity could contribute to the decline in $\dot{V}O_{2\,max}$ with aging, and that this effect becomes more relevant in senescence. This latter point is important because human studies of the factors contributing to a decline in $\dot{V}O_{2\,max}$ in subjects older than 75 years of age are essentially non-existent.

Mitochondria is an important focus for aging research, with countless studies documenting age-related changes in tissues from brain (Lenaz et al. 1997), to liver (Harper et al. 1998), to heart (Wanagat et al. 2002), to skeletal muscle (Coggan et al. 1992*b*). Since mitochondria in skeletal muscle are so adaptable in response to increases or decreases in muscle use (Baar et al. 2002; Coyle et al. 1984; Holloszy 1967), a very relevant question concerns the extent to which a decline in mitochondrial oxidative capacity with aging is due to a lower mitochondrial volume (as would be expected to occur with more sedentary lifestyle) versus poorer-functioning mitochondria. Before addressing this question it should be noted that findings regarding age-related changes in skeletal muscle mitochondrial oxidative capacity vary considerably. Whereas a number of human studies support the idea that skeletal muscle mitochondrial oxidative capacity declines with aging (Coggan et al. 1992*a*; Rooyackers et al. 1996; Tonkonogi et al. 2003), including one that utilized a very large number of subjects (Short et al. 2005), other studies find no decline (Orlander and Aniansson 1980; Rasmussen et al. 2003). It seems likely that much of the discrepancies in this respect can be traced to differences in physical activity levels of the subjects because there are many studies showing that the mitochondrial oxidative capacity retains the capacity to improve with exercise training at least into the seventh decade of life (Coggan et al. 1992*b*; Meredith et al. 1989; Short et al. 2003). It should be noted, however, that one need not see a decline in muscle oxidative capacity for there to be a reduction in mitochondrial function with aging; maintained oxidative capacity could represent compensation by increasing mitochondrial content to offset declines in function.

One of the first indications that skeletal muscle mitochondria may exhibit impaired function with aging comes from the observation that cytochrome oxidase is often seen to exhibit a preferential decline in activity in aging muscles (Hepple et al. 2005, 2006; Tonkonogi et al. 2003). This phenomenon is observed in many tissues (Navarro and Boveris 2007), underscoring the likelihood that it relates to an aging effect. Another indication of mitochondrial dysfunction in aged skeletal muscles is the observation that a previous

Fig. 6. $\dot{V}O_{2\,max}$ (grey bars) in skeletal muscles of young adult (8–9 months), late middle-aged (28–30 months), and senescent (36 months) Fischer 344 × Brown Norway F_1 hybrid rats perfused in situ at matched rates of muscle convective oxygen delivery ($\dot{Q}O_2$, black bars). Reproduced with permission from Hagen et al. J. Gerontol. Biol. Sci. **59A**(11): 1099–1110. ©2004 The Gerontological Society of America.

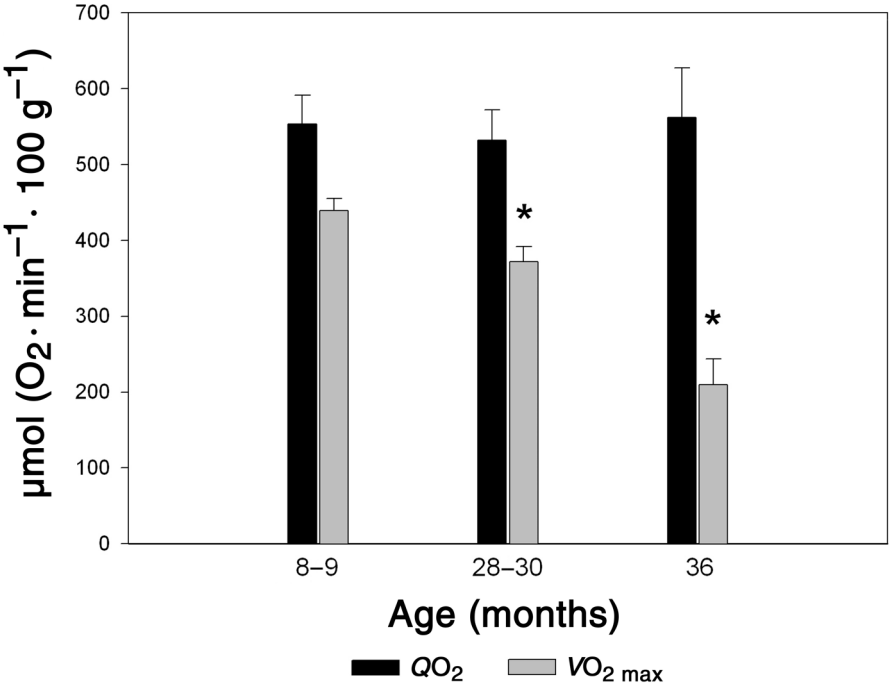
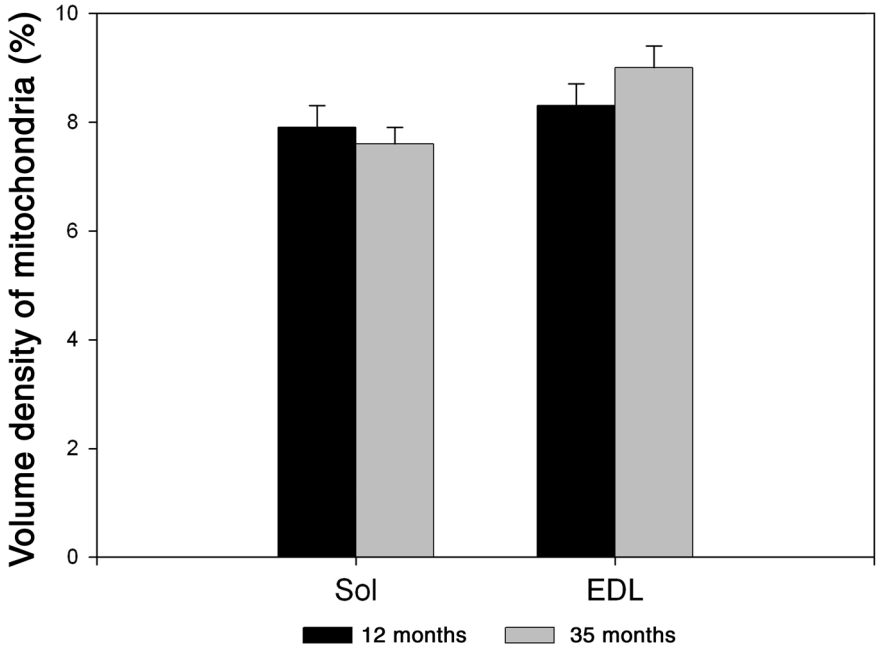
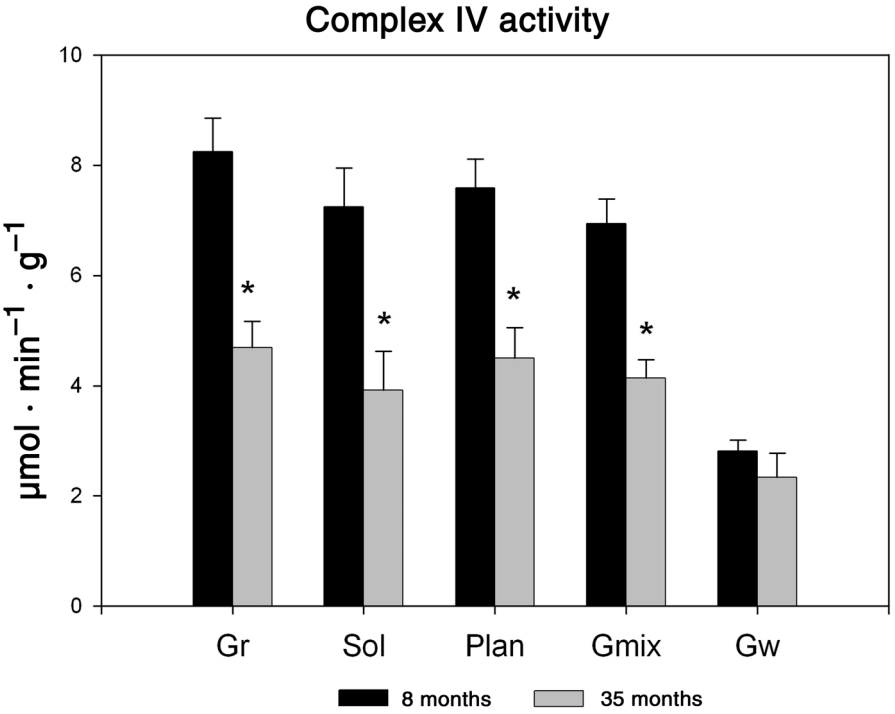


Fig. 7. Mitochondrial volume density in slow-twitch soleus (Sol) or fast-twitch extensor digitorum longus (EDL) muscles of young adult (12 months) and senescent (35 months) Fischer 344 × Brown Norway F_1 hybrid rats. Adapted from Mathieu-Costello et al. (2005).



study observed no decline in mitochondrial volume density in either slow- or fast-twitch muscles with aging (Mathieu-Costello et al. 2005) (Fig. 7), despite the fact that another study has shown declines in cytochrome oxidase activity in both slow- and fast-twitch muscles in the same animal model studied at the same age (Hepple et al. 2006) (Fig. 8). There is also at least one study showing a dissociation of enzyme activities and enzyme protein levels in aged muscles (Bota et al. 2002), and another showing a larger decline in muscle oxidative function than mitochondrial volume density in aged humans (Conley et al. 2000). Therefore, on the basis of this evidence, a decline in skeletal muscle mito-

Fig. 8. Cytochrome oxidase activity in crude homogenates of red gastrocnemius (Gr), soleus (Sol), plantaris (Plan), mixed gastrocnemius (Gmix), and white gastrocnemius (Gw) muscles of young adult (8–10 months; black bars) and senescent (35–36 months; grey bars) Fischer 344 × Brown Norway F_1 hybrid rats. Adapted from Hepple et al. (2005).



chondrial oxidative capacity with aging is due at least in part to mitochondrial dysfunction, whereas a decline in mitochondrial content seems a lesser concern. We will not consider the causes of this dysfunction at this point, since the issue remains to be resolved and several investigators continue to explore this important question.

Perspectives on the significance of changes in oxygen delivery versus oxidative capacity across the aging continuum

The decline in $VO_{2\,max}$ with aging is caused by many factors, but, interestingly, not all factors may contribute equally across the life span. For example, the available evidence suggests that declining muscle blood flow (Poole et al. 2003; Proctor et al. 1998*a*; Wahren et al. 1974), consequent to a decreased maximal cardiac output and potentially a maldistribution of that output (Proctor et al. 1998*a*, 1998*b*), contributes to the majority of the age-related decline in $VO_{2\,max}$ in subjects up to 65 years of age. This point is made on the basis of the abundance of data showing significant reductions in maximal cardiac output and muscle blood flow noted above, versus the only mild decline in $VO_{2\,max}$ seen in rat hindlimb muscles of late middle-aged animals pump-perfused at similar levels of muscle oxygen delivery as those of young adult animals (Hagen et al. 2004). In contrast to this, it appears likely that alterations within the contracting skeletal muscles contribute more meaningfully to the decline in $VO_{2\,max}$ into the senescent period and beyond (i.e., 80 years of age and older in humans). This point is based on the fact that senescent rat muscles pump-perfused at similar levels of muscle oxygen delivery as those of young adult rats exhibit an approximately 50% lower $VO_{2\,max}$ (Hagen et al. 2004). Thus, it is clear that even if one were to restore cardiac output and muscle blood flow to levels seen in young adults, senescent muscle would be incapable of using sufficient oxygen to recover $VO_{2\,max}$ to values anywhere near those seen in young adults. This marked performance decline within the aging muscles in senescence likely contributes to the acceleration of $VO_{2\,max}$ decline in senescence (Fleg et al. 2005; Olfert et al. 2004). Strikingly, it appears that alterations within the microvasculature, particularly in the context of the anatomic determinants of capillary supply (Croley et al. 2005; Hepple and Vogell 2004; Mathieu-Costello et al. 2005; Ryan et al. 2006), do not put aged muscles at a disadvantage relative to those of young adults. These observations underscore the integrated nature of the $VO_{2\,max}$ response and the point that, to fully comprehend the physiological basis for the age-related $VO_{2\,max}$ decline, one needs to take into account both the capacity for oxygen delivery to and its use by skeletal muscle.

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