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Altered microvascular control of exercising skeletal muscle blood flow: the unfortunate male?

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During dynamic exercise there is an increased metabolic demand that is matched closely by increased skeletal muscle blood flow and oxygen delivery. Ageing is associated with a variety of adaptations within the cardiovascular system that can compromise muscle blood flow or alter its regulation during dynamic exercise. Some of these adaptations include a reduced cardiac pump capacity, structural alterations in the vasculature, alterations in local vascular control mechanisms, and increased muscle sympathetic neural outflow. Collectively these changes contribute to a decline in the capacity to regulate skeletal muscle blood flow, which may play a role in the age-related reductions in maximal oxygen consumption and physical function.

To date, the majority of the studies comparing muscle blood flow and vascular control in exercising young and older humans have only assessed limb haemodynamics once steady-state exercise has been achieved. Although this approach has provided fundamental information on the regulation of skeletal muscle blood flow across a range of exercise intensities and under various conditions, it has often ignored the immediate vasodilator response to muscle contraction. In this context, the mechanisms influencing vascular tone at the onset of exercise may be different than those involved in the control during steady-state exercise. Furthermore, ageing might impact one variable more than the other. There is evidence that muscle blood flow increases, via vasodilatation immediately, following single muscle contraction in young adults. In contrast, this vasodilatory response is substantially attenuated with ageing (Carlson *et al.* 2008). While these findings suggest that vascular regulation within the microcirculation is impaired with ageing, methods commonly used to study limb blood flow in humans are limited to more proximal arteries (i.e. conduits) and do not allow for the direct assessment of vasomotor function in the microvasculature. Therefore, in a recent study in *The Journal of Physiology*, Jackson *et al.* (2010) investigated how ageing influences the arteriolar control of blood flow within a mammalian hindlimb muscle and determined whether sex influenced the vasodilatory response to muscle contraction.

The authors hypothesized that ageing would impair rapid onset vasodilatation (ROV) in 2nd order distributing arterioles (2A) of mice. To test this hypothesis in an isolated gluteus maximus preparation, 2A diameters at rest and after single tetanic contractions in 20-month-old male and female C57BL/6 mice were compared to those of 3-month-old male and females using intravital microscopy. In the older males the ROV was reduced by ∼50% compared to the other three groups. In addition to the reduction in dilatation, ageing was also associated with an attenuated blood flow response.

In light of these observations and to further understand the mechanisms behind the impairment in older males, Jackson *et al.* subsequently investigated the influence of α-adrenergic vascular tone on microcirculatory changes to contractile activity. Interestingly, blockade of α-adrenoreceptors with phentolamine restored ROV in the older males to similar levels observed in the other groups. Yet when phentolamine was administered to age-matched females and young males there were no changes in ROV. Conversely, when topical noradrenaline was administered to young mice, ROV was blunted to a level similar to that seen in older males. Moreover, when noradrenaline (norepinephrine) was given to the older males, ROV was further decreased. Thus, these results suggest that impaired vasodilatory responses at the microcirculatory level in older males are due to vasoconstrictor restraint by increased α-adrenoreceptor activation.

To determine if similar responses are elicited by rhythmic contractions, the authors examined the vasodilatory and blood flow response to steady-state exercise (i.e. 30 s of contractions). In contrast to the single contractions, 2A vasodilatation was similar between older and younger male mice during rhythmic exercise. Despite similar vasodilatation, arteriolar blood flow was 2–3 times larger in young males compared to older males. Unfortunately, the vasodilatory and blood flow response were not investigated in either young or older female mice.

The main novel findings of Jackson *et al.* are that ageing (1) blunts the immediate vasodilatory and blood flow response to single tetanic contractions within the skeletal muscle microvasculature of male mice and (2) is associated with constitutively elevated levels of α-adrenergic receptor activation that consequently restricts ROV in resistance microvessels of older male mice. However, ageing does not blunt 2A dilatations during rhythmic submaximal contractions despite an attenuated arteriolar blood flow in older male mice. From these findings, Jackson *et al.* concluded that the proximal segments of the resistance vascular network are key sites for restricting muscle blood flow with ageing and is probably a result of increased vascular α-adrenoreceptor activation.

Jackson *et al.* indicate that ROV in older male mice was blunted due to activation of the α-adrenergic receptors, which may be due to higher levels of sympathetic nerve activity that occur with age. However, the older female mice did not have a reduced ROV compared to the younger female mice. We were specifically interested in this finding; since in humans, females also demonstrate age-related increases in sympathetic nerve activity as they age (this increase can be greater than their male counterparts). Thus, if α-adrenergic receptor activation does limit ROV it would be expected that the older female mice would also have a decreased dilatory response to single contractions. Along these lines, in humans, Parker *et al.* (2008) demonstrated that older females had a greater impairment in exercise-induced vasodilatation *vs.* older men, which was abolished when data were scaled for quadriceps muscle mass.

There could be several explanations for the similar ROV in the older and young female mice. First, the older female mice may have a large reduction in α-adrenergic

DOI: 10.1113/jphysiol.2010.195800

receptor sensitivity compared to the older male mice. Thus, in the older female mice, the net effect of higher levels of sympathetic nerve activity on ROV would be minimal and result in a similar level of α-adrenergic receptor activation as the young female mice. However, whether α-adrenergic receptor sensitivity is reduced in ageing females remains to be elucidated. Second, it is possible that there is enhanced β-adrenergic receptor sensitivity to noradrenaline in females (Kneale *et al.* 2000). Consequently, increases in sympathetic nerve activity may not restrain ROV via α-adrenergic receptor activation, because concomitant β-adrenergic receptor activation offsets α-mediated constriction. Nonetheless, whether the higher sensitivity of the vascular β-adrenergic receptor persists in females as they age is unknown. It appears that the higher sensitivity of the β-adrenergic receptors in females may be associated with oestrogen; however, in the study by Jackson *et al.* it was not stated if the female rats were menopausal. Finally, whether sympathetic nerve activity is increased with ageing in this strain of female mice is unknown. Therefore, sympathetic nerve activity and α-adrenergic receptor activation may have been similar in the older and younger female mice. Furthermore, we do not know what the basal level of sympathetic outflow was in the groups of anaesthetised mice. The anaesthetic used may have affected basal sympathetic outflow differently in each group and thus makes these data hard to apply to 'awake' animals.

Interestingly, Jackson *et al.* showed that ageing did not attenuate 2A dilatation during rhythmic twitch contractions. However, older male mice demonstrated significantly lower arteriolar blood flow as compared to their younger counterparts. Thus, the reduced blood flow during submaximal exercise in aged male mice was probably a result of a blunted ability to evoke dilatation in proximal segments of the resistance network. However, the authors did not measure whether blood flow was improved during rhythmic contractions in the older male rats after phentolamine administration. Thus, we do not know whether increased α-adrenergic receptor activation in the proximal arteries restrains blood flow in older male rats during rhythmic exercise. These data would add key information regarding the control of skeletal muscle blood flow during exercise. In addition, alterations in the topology of the arteriolar network may help to explain the blunted blood flow responses to rhythmic exercise in the older male mice. Previous data from the same laboratory suggest that in the arteriolar networks from the gluteus maximus of ageing male mice, the distal vessels become more tortuous and the vessel branch angles increase (Bearden *et al.* 2004). Accordingly, these changes in vasculature of ageing male mice may increase the resistance of the distal arterioles to blood flow and thus blunt increases in blood flow during rhythmic exercise.

Since there was a differential response of blood flow in the aged male mice to rhythmic and single contractions, these findings suggest that the effect of ageing on arteriolar dilatation depends on the nature of contractile activity, and the signalling events mediating sustained vasodilatation differ from those mediating rapid vasodilatation. One potential mechanism for microvascular dysfunction with ageing that was surprisingly not discussed by Jackson and colleagues was alterations in endothelial-mediated vasodilatation. Along these lines, recent data suggest that the time course and magnitude of endothelium-dependent vasodilatation in isolated arterioles is significantly slower and reduced in skeletal muscle of old rats (Behnke & Delp, 2010). Therefore, an age-associated blunting of endothelial-dependent vasodilator dynamics provides a plausible mechanism for the reduced blood flow during sustained rhythmic muscle contractions.

In conclusion, Jackson *et al.* provide a novel insight into the mechanisms on how age and sex impact microvascular control of exercising skeletal muscle blood flow. The authors should be commended on their approach to examine the regulation of blood flow in the contracting muscle at the microvascular level and highlighting the influence of age as well as sex on these responses. Future studies might aim to examine whether similar changes with age and sex exist in different muscle groups. For example, (Musch and colleagues (2004) demonstrated that despite similar increases in total hindlimb blood flow in young and old rats during submaximal exercise, there are differences in blood flow distribution between highly oxidative and highly glycolytic muscles. Additionally, since the vasodilatory response was sex specific in the older mice, it is interesting that the steady state measurements were not performed in older females and could be considered in follow-up studies.

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Acknowledgments

The authors apologize for not citing all relevant articles due to reference limitations.