Setting the “tone” for aging in the skeletal muscle microcirculation

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The ability to regulate vasomotor tone in resistance arteries and arterioles plays an integral role in mediating the circulatory adjustments that occur during exercise. During exercise, skeletal muscle blood flow must increase to actively contracting skeletal muscle to supply oxygen and nutrients and to remove metabolic waste products. The exercise-induced increase in skeletal muscle blood flow, as well as the redistribution blood flow within and between muscle fibers, is determined in large part by a reduction in vasomotor tone (i.e., vascular resistance) in arteries and arterioles perfusing the actively contracting muscle. An impaired ability to properly reduce vasomotor tone in active skeletal muscle during exercise may result in an impaired ability to augment blood flow and reduce exercise capacity.

One population at risk for vascular cell dysfunction, leading to an impaired ability to regulate vasomotor tone, is the elderly. The age-induced vascular cell dysfunction in the skeletal muscle vascular beds has been proposed to contribute to impaired muscle blood flow responses to exercise and to a reduction in exercise tolerance (1, 7, 8). Although the mechanisms accounting for the age-related changes in vascular cell function are not fully understood, a series of studies by Muller-Delp and colleagues has provided valuable insight into vascular cell aging in the skeletal muscle microcirculation.

At least two mechanisms have been proposed to contribute to the age-related decrement in exercise hyperemia. First, aging may induce vascular cell adaptations, resulting in enhanced responsiveness of the skeletal muscle arterioles to vasoconstrictor stimuli. Second, aging may induce vascular cell adaptations resulting in an impaired ability of arterioles to respond to vasodilator stimuli. If true, the balance between vasoconstrictor and vasodilator influences may be shifted in favor of enhanced vasoconstrictor tone in aged arterioles, resulting in an impaired ability to augment muscle blood flow during exercise. To test the first hypothesis, Muller-Delp et al. (5) used an isolated arteriole preparation to determine the effects of aging on vasoconstrictor responses of first order arterioles from the soleus and gastrocnemius muscle of Fischer 344 rats. Results revealed that vasoconstrictor responses to norepinephrine and potassium chloride were similar in arterioles isolated from the soleus and gastrocnemius muscles of young (4 mo) and old (24 mo) rats. Thus, contrary to their hypothesis, aging was not associated with enhanced vasoconstrictor responsiveness in skeletal muscle arterioles (5).

To test the second hypothesis, these researchers used isolated arterioles to determine the effects of aging on vasodilator responses in first order arterioles (4). Results of the study revealed that endothelium-dependent dilation induced by increases in intraluminal flow was impaired in arterioles isolated from the soleus and gastrocnemius muscles. Importantly, Muller-Delp and colleagues found that vasodilator responses to ACh were impaired in arterioles from the soleus (but not gastrocnemius) muscle. Similar findings of muscle-specific vascular adaptations to aging have been reported in feed arteries perfusing skeletal muscles of aged rats (10). Thus it appears that age-induced vascular adaptations in the skeletal muscle vasculature occur in a nonuniform fashion characterized by more profound dysfunction in arterioles perfusing oxidative skeletal muscle than in muscle composed primarily of glycolytic fibers. In addition, the age-related decrements in endothelium-dependent vasodilator responses in skeletal muscle feed arteries and arterioles may work in concert to impair the ability to increase muscle blood flow during exercise. This speculation is supported by previous studies indicating that muscle blood flow responses to exercise are blunted in oxidative muscles, whereas blood flow to glycolytic muscles is preserved or enhanced in old rats (6).

To begin to elucidate the mechanisms accounting for the age-related decline in endothelium-dependent dilation in skeletal muscle arterioles, Muller-Delp et al. (4) examined vasodilator responses in the absence and presence of enzymatic inhibitors of the known endothelium-dependent vasodilator pathways. Results indicated that the mechanism for the age-related decline in vasodilator responses differed in soleus and gastrocnemius arterioles. Specifically, diminished endothelium-dependent vasodilator responses in soleus arterioles resulted from a decrease in nitric oxide-mediated dilation, whereas in the gastrocnemius, adaptation of the endothelium appeared to occur through an alternate pathway. These findings are important in part because they highlight the functional heterogeneity in the vascular adaptations to aging and reveal that results obtained from a single artery or arteriole cannot be generalized to all vascular beds.

In the present issue of the Journal of Applied Physiology, Muller-Delp and colleagues (2) expanded on their previous studies related to endothelial cell adaptations to aging in the skeletal muscle microcirculation by studying age-induced adaptations in vascular smooth muscle. Specifically their study was designed to begin to determine the mechanisms accounting for the age-related impairment of myogenic reactivity in skeletal muscle arterioles. Since the myogenic response plays a central role in regulating peripheral vascular resistance and tissue specific blood flow, understanding the mechanisms accounting for the age-induced deficit is an important endeavor.

In their study, Kang et al. (2) used isolated arterioles to determine the relative contributions of large conductance (BKCa) and voltage-dependent (KV) K+ channels to the regulation of myogenic tone in skeletal muscle arterioles. The authors report four main findings. First, myogenic responses were blunted by aging in skeletal muscle arterioles. Second, KV channels contributed to the age-associated reduction of the myogenic response in skeletal muscle arterioles. Third, in...
soleus muscle arterioles the age-related decline in myogenic constriction was due in part to increased modulation of myogenic activity by BKCa channels. Fourth, the contribution of Kv and BKCa channels to the regulation of myogenic tone varied in skeletal muscle arterioles from muscles of different fiber type. Since the myogenic response plays an important role in maintaining local blood flow and total peripheral resistance, these authors propose that the age-related decline in myogenic responsiveness may contribute to the decrements orthostatic tolerance (3) and exercise capacity (1) observed in aged individuals.

Through innovative studies like these, Muller-Delp and associates have established themselves as leaders in the field of vascular biology of aging. The overriding theme of their research is that age-induced vascular cell adaptations in both endothelial and vascular smooth muscle cells result in an impaired ability to regulate vascular tone. This age-associated defect in vascular function is clinically relevant in that it may contribute to the reduction in exercise tolerance and the orthostatic intolerance observed in the elderly. Whether these vascular adaptations are due to the primary effects of aging or are secondary to changes in physical activity is not known; however, central to the rationale of the research coming from the Muller-Delp laboratory is the hypothesis that age-related decrements in vascular function are a consequence of physical inactivity rather than to a primary effect of aging on vascular cell phenotype. If this hypothesis is correct, interventions directed toward increasing physical activity may attenuate or reverse the detrimental effects of aging on vascular cell function in the skeletal muscle microcirculation. In support of this hypothesis, Muller-Delp and colleagues recently reported that age-induced endothelial dysfunction in skeletal muscle arterioles can be reversed by a program of exercise training. A protective effect of exercise has also been reported in feed arteries perfusing aged skeletal muscle (9). Future studies will be needed to determine whether exercise training reverses the effect of aging on myogenic responses in the skeletal muscle microcirculation. In addition, studies are needed to determine the signals associated with exercise that modulate vascular cell function in aged arteries.

REFERENCES