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MECHANISMS FOR EXERCISE TRAINING-INDUCED INCREASES IN SKELETAL MUSCLE BLOOD FLOW CAPACITY: DIFFERENCES WITH INTERVAL SPRINT TRAINING VERSUS AEROBIC ENDURANCE TRAINING

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Skeletal muscle blood flow capacity (BFC) is increased by exercise training due to structural vascular remodeling (in the form of angiogenesis of capillaries and remodeling of the arterial tree within skeletal muscle) and/or altered control of vascular resistance. Changes in control can be central or the result of changes in reactivity of arteries and arterioles (due to changes in vascular smooth muscle and/or endothelium). The purpose of this review is to evaluate the relative importance of these mechanisms for increased BFC following interval sprint training (IST) and endurance exercise training (ET). Based on the results discussed herein we conclude that the importance of each of these mechanisms varies throughout muscle tissue due to interactions of muscle fiber-type composition and muscle fiber recruitment patterns during exercise. The distribution of vascular adaptive changes varies with mode of training. For example, IST has been shown to produce the greatest relative increase in contractile activity in fast-twitch, white, skeletal muscle (*i.e.* white gastrocnemius muscle (Gw) and Gw muscle exhibits the largest increase in oxidative capacity, capillary density, BFC, and changes in vascular cells with IST. In contrast, ET has been shown to produce the greatest relative increase in contractile activity in red gastrocnemius muscle (Gr), and Gr muscle exhibits the largest increase in oxidative capacity, capillary density, and BFC after ET training. Results demonstrate that the increases in BFC are not mediated solely by structural adaptation. Rather, changes in vascular control predominate in Gr and soleus muscle, while increases in arteriolar and capillary density predominate following IST in Gw. Finally, evidence indicates that ET and IST induce non-uniform changes in smooth muscle and endothelium throughout skeletal muscle arteriolar networks.

Key words: *blood flow, capacity, vascular remodeling, exercise*

INTRODUCTION

Exercise training improves cardiovascular function and increases vascular transport capacity of skeletal muscle (1-4). In human subjects exercise training for as little as 4 weeks has been reported to increase blood flow capacity (BFC) as measured by reactive hyperemic responses to occlusion of blood flow to the forearm (5, 6). Also, Volianitis and colleagues (7) report that the BFC of elite rowers, as measured from maximal arm vascular conductance, was 35% greater than in average fit subjects and more recently, highly trained cyclists have been reported to have greater BFC of the legs, as reflected in increased reactive hyperemic flow (8). Animal experiments also indicate that increased levels of physical activity alter skeletal muscle exercise hyperemia, indeed both maximal cardiac output and muscle blood flow are increased by exercise training (9-11). For example, Musch and colleagues reported that endurance exercise training of dogs produced a 30% increase in maximal cardiac output and that 80% of this additional cardiac output was distributed to skeletal muscle (12). Understanding mechanisms responsible for exercise training-induced increases in skeletal muscle blood flow capacity (BFC) and increased skeletal muscle blood flow during natural exercise requires integration of knowledge about skeletal muscle fiber type composition, muscle fiber recruitment patterns during exercise, distribution of blood flow within and among muscles, and anatomy of skeletal muscle vascular beds.

The purpose of this brief review is to summarize what is known about exercise training-induced vascular adaptative mechanisms that contribute to increased BFC in skeletal muscle. As summarized below, current evidence indicates that exercise training induces increases in BFC by at least two primary mechanisms: 1) structural remodeling of the vascular tree (capillary bed and arterial tree) and by 2) altered vasomotor reactivity of arteries and arterioles; *i.e.* altered control of conductance. Muscle fiber type composition exerts powerful influences on vascular structure and function in, and on the biological strategy for, vascular adaptation of skeletal muscle (13-15). Given the importance of muscle fiber type, our strategy for this review is to first summarize and discuss skeletal muscle fiber type composition and how it impacts the vasculature. Then we summarize and discuss current state of knowledge concerning the contribution of structural vascular adaptation to training induced increases in BFC. Next we review the contribution of altered control of vascular resistance mediated through changes in endothelium and vascular smooth muscle. Finally we integrate these data to summarize how current information indicates that exercise training increases BFC in skeletal muscle.

SKELETAL MUSCLE FIBER TYPE AND VASCULAR STRUCTURE AND FUNCTION

Skeletal muscle is a complex tissue composed of connective tissue, nerves and muscle fibers. Muscle fibers have been grouped into 3 general phenotypes based on

their contractile and metabolic properties (16): slow-twitch oxidative (SO) fibers, fast-twitch, glycolytic (FG) fibers, and fast-twitch, oxidative, glycolytic (FOG) fibers. The remarkable matching of vascular structure and function to muscle fiber characteristics has been demonstrated in a number of mammalian species, ranging from rat to man (15-19). The relationships among muscle fiber type, oxidative capacity, vascularization, capillary exchange capacity, mechanisms of vascular control, muscle fiber recruitment patterns during exercise, and regional distribution of blood flow within and among muscles during exercise are well recognized (4, 17, 20-23). For example, it is well established that muscles composed predominantly of slow-twitch fibers have increased capillarization, arteriolar density, oxidative capacity, and endothelium-dependent dilation when compared with white muscle composed mainly of fast twitch fibers (4, 14, 17, 24-26).

MUSCLE FIBER RECRUITMENT PATTERNS DURING EXERCISE: IMPLICATIONS FOR TRAINING-INDUCED VASCULAR ADAPTATIONS

Muscle fiber recruitment during exercise occurs in a reasonably predictable manner depending on duration and intensity of exercise (4, 27, 28). In general, at low intensities, deep, high-oxidative fibers, SO and FOG, are recruited and produce the majority of force, while at increasing intensities, fast-twitch fibers are recruited progressively, so that during high-intensity exercise (sprints) all fibers are active. As expected, this recruitment pattern directly impacts muscle blood flow responses to exercise (4, 28). Thus, during an acute bout of exercise the increase in muscle blood flow: 1) is distributed heterogeneously within and among skeletal muscles (4, 17, 29), 2) is related to muscle fiber type and muscle fiber recruitment patterns (4, 17) and 3) changes within and among muscles over time during sustained submaximal exercise, due to changes in muscle fiber recruitment patterns (4, 17). Together, these observations importantly highlight the notion that given an exercise intensity, the metabolic milieu surrounding the resistance arteries, and the physical forces to which the vasculature is exposed may vary considerably in different portions of the muscle and between muscles. As discussed below, it is therefore conceivable that exercise training-induced vascular adaptations are distributed non-uniformly, not only between muscles of different fiber type composition, but also within the same vascular network. We next, review the evidence of structural changes in skeletal muscle vasculature associated with exercise training.

STRUCTURAL VASCULAR ADAPTATIONS

There is strong support in the literature for the concept that exercise training-induced structural and functional changes are concentrated in the muscle tissue having the greatest increase in activity during each training session (*Fig. 1*) (9, 30-35). For example, interval sprint training (IST) (high speed, uphill running)

produces the greatest relative increase in contractile activity in fast-twitch, white skeletal muscle, like Gw (29, 36) and this type of training produces the largest relative increase in oxidative capacity (36), capillary density (31) and BFC, in Gw muscle (30, 34, 35). In contrast, endurance exercise training produces the greatest relative increase in contractile activity in Gr muscle. Also, Gr muscle exhibits the largest relative increase in oxidative capacity (36), capillary density (31) and BFC of the extensor muscles examined in rats following endurance exercise training (30, 34, 35). Available results indicate that capillarity increases in the soleus and Gr muscles of ET rats and that capillarity is increased only in the Gw muscle of IST rats (31, 32). However, the limited magnitude of these changes in capillarity indicates that increases in BFC of these muscle tissues following training are not mediated solely by increased capillarization (31, 35).

CAPILLARY ANGIOGENESIS; EXERCISE TRAINING INDUCES NON-UNIFORM INCREASES IN CAPILLARITY

Exercise training increases the number of capillaries per square millimeter of muscle in humans and these increases are greatest in SO (Type I) and FOG (Type IIA) skeletal muscle (37-39). Results from exercise trained rats indicate that exercise training-induced angiogenesis of capillaries within and among skeletal muscles is greatest in the muscle tissue with the greatest relative increase in fiber activity during training bouts (30-32, 34-36, 40, 41). Analysis of different types of exercise training on capillarity in different regions of the gastrocnemius muscle reveals that exercise training-induced adaptations of capillarity and mitochondrial content are spatially coupled so that the regions that exhibit increased oxidative capacity also exhibit increased capillarity (15, 31, 32). That is, ET increases capillarity in high oxidative skeletal muscle, such as Gr, but not in low oxidative muscle, such as Gw (15, 32). In contrast, capillarity is increased in Gm and Gw by IST but not in high oxidative muscle tissue (31). It seems reasonable to conclude that adaptations of BFC, capillarity and oxidative capacity are coupled spatially within and among muscles (15). On the other hand, while the regional distribution of training-induced adaptations of BFC, capillarity, and oxidative capacity appear coupled spatially in the muscle, the magnitude of these adaptations within and among skeletal muscles are not. For example, IST induces 3 fold increases in oxidative capacity, 2 fold increases in BFC, and only 20% increases in capillarity of Gw (30-32, 34-36, 40, 41).

ARTERIOLAR DENSITY; EXERCISE TRAINING INDUCES NON-UNIFORM INCREASES IN ARTERIOLAR DENSITY IN SKELETAL MUSCLE

Increased BFC can result from increased maximal vascular conductance resulting from increased arteriolar density (increased number and/or size of

arterioles). Thus, vascular remodeling of the arteriolar tree could play a role in the increases in BFC in both red and white portions of the gastrocnemius muscle. Results in rats indicate that ET increases BFC in Gr, Gm, Gw, and soleus (42). ET also appears to increase arteriolar density throughout fast twitch skeletal muscle, as reflected in increases in both the Gw and Gr, but in contrast, soleus muscle arteriolar density was not significantly altered (43). This same study reported that ET did not alter wall thickness of skeletal muscle arterioles.

The increase in arteriolar density in Gw caused by ET appeared to be the result of an increase in the number of arterioles in the size range of 8-20 μm diameters with no change in the number of smallest arterioles or arterioles larger than 25 μm. In contrast, in Gr muscle tissue, the increase in arteriolar density with ET was the result of an increase in the number of arterioles of larger diameter (16 to > 25 μm diameter) (43). In opposition to these ET effects on arteriolar density, IST did not alter arteriolar density, % artery area, total artery area, or arteriolar wall thickness in either the Gw, Gr, or soleus muscle tissue (43). This result was surprising because Gw muscle of similarly trained rats exhibited a 30% increase in BFC (30). Interestingly, BFC of mixed gastrocnemius muscle (Gm) was increased by nearly 100% in these same IST rats (30). Because arteriolar density in Gm muscle was not examined in the study of Laughlin *et al*. (43), we conducted a study to determine whether arteriolar density is increased in Gm muscle of IST rats. Arteriolar densities and dimensions were measured using vascular casting techniques and computational network model analysis was used to examine mechanisms responsible for increased skeletal muscle blood flow capacity in Gm muscle tissue of IST rats (44). The results of this study revealed that the number of arterioles of branch order 3A through 6A were increased by IST in Gm muscle while arteriolar length and diameter per arteriolar order were unchanged by IST training. The computational model analysis predicted that this arteriolar remodeling would shift the primary site of vascular resistance from 3A arterioles (in sedentary rats) to the 5A and 6A arterioles in IST rats. Importantly, the model analysis also indicated that these changes in the arteriolar tree of the Gm muscle tissue would be sufficient to create the doubling of BFC reported for Gm muscle of IST rats (30, 44). This is of great interest because, as discussed above, previous findings with IST training of rats indicated that BFC increases were not coupled to increased capillarity. Thus this study indicates that structural arteriolar remodeling may be the primary adaptation responsible for the IST-induced increase in BFC in Gm muscle (44).

Available information does not support the hypothesis that increases in arteriolar density are focused in the tissue with the greatest increase in activity during training bouts (*i.e.* soleus and Gr muscle tissue with ET and Gw with IST). ET has the greatest effects on fiber activity, oxidative capacity and capillary density in Gr muscle but ET doubled arteriolar density in both Gr and Gw muscle and did not alter arteriolar density in soleus muscle (43). In contrast to the similar increase in arteriolar density of Gr and Gw after ET (43), Gute and colleagues (32)

reported that ET increased capillarity by 50% in Gw muscle, 55% in Gm muscle, and by 27% in Gr muscle. Thus, while ET appears to increase both arteriolar and capillarity throughout the gastrocnemius muscle, the increase in arteriolar density is similar in Gr and Gw while the changes in capillarity are greater in Gw and Gm than in Gr. In contrast, available results from soleus muscle indicate that ET increases BFC without altering arteriolar or capillary density (31, 43). Clearly the increase in BFC of soleus muscle after ET is therefore the result of altered control of vascular resistance. Further, the greater increase in BFC of soleus and Gr than Gw and increases in capillarity and arteriolar density of Gm and Gw muscle reported after ET, suggest that adaptations in vasomotor control of resistance may be a major influence in increased BFC of Gr with ET as well (42, 43).

MECHANISTIC BASIS OF EXERCISE-INDUCED VASCULAR REMODELING

Controversy continues concerning what signals vascular adaptation in skeletal muscle in response to exercise. The most popular proposals are that mechanical forces (such as shear stress or muscle stretch) or that metabolic signals activate vascular adaptation to exercise (45). Recently, Hellsten and co-workers provided evidence in humans that muscle stretch and the related increase blood flow might be a signal for training-induced vascular adaptations. Using a model of knee extension, these authors have shown that 90 minutes of passive exercise acutely increased VEGF release in muscle interstitium as well as increased eNOS mRNA in muscle tissue, without any appreciable effects on muscle metabolism (46).

An important and often unappreciated issue in the study of the mechanistic basis of vascular remodeling after training is that the signals and/or factors promoting angiogenesis might be different than those inducing arteriogenesis. In fact, contrary to our hypothesis that adaptations in arteriolar density would reflect reported adaptations of capillarity (31, 32), we found strikingly different spatial patterns of adaptation of these factors within and between muscles (see *Fig. 1*). Along this line, there is considerable evidence that, in rat skeletal muscle, the anatomical processes responsible for formation of new capillaries (sprouting and/or intussusception) are different from processes responsible for formation of new arterioles. Price and Skalak (47, 48) have shown that during normal maturation and in response to chronic prazosin treatment, new arterioles form when capillaries become invested with smooth muscle. Direct evidence lacking, the role of "capillary arterialization" in vascular adaptation induced by exercise training in skeletal muscle has yet to be established.

In conclusion, while structural vascular adaptation can explain changes in BFC produced by IST training, structural vascular adaptation does not account for the increases in BFC produced by endurance training. The fact that increases in BFC in exercise trained skeletal muscle are not fully explained by structural adaptations (*i.e.* increased capillarity, increased arteriolar number or sizes) indicates that control of vascular resistance and vasomotor responses mediated by

endothelial cells and/or smooth muscle cells must also contribute to increased BFC in trained skeletal muscle (30-32, 34, 35, 41).

FUNCTIONAL VASCULAR ADAPTATION; CHANGES IN CONTROL OF CONDUCTANCE

The investigation of how the mechanisms controlling vascular conductance during exercise are modulated by exercise training has been partially impeded by the incomplete understanding of which signals and/or factors govern muscle blood flow responses to exercise.

The exhaustive search for a unifying hypothesis to explain mechanisms of exercise hyperemia has strengthened the concept of redundancy and it is now well

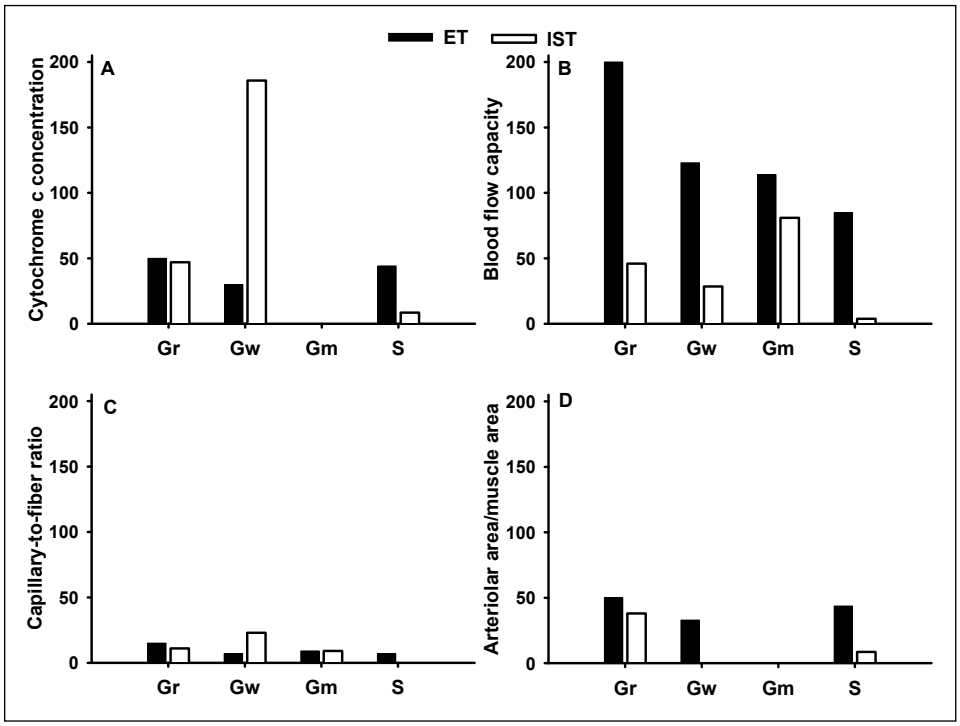

Fig. 1. Relative changes in: A) oxidative capacity (as reflected in measures of cytochrome c concentration), B) blood flow capacity, C) capillary to fiber-ratio, and D) arteriolar area/muscle area in rat muscles after endurance training (ET) and interval sprint-training (IST). All data are expressed as a % increase above the respective SED value (ET value = ET-SED/SED x 100% and IST value = IST-SED/SED x 100%). ET program consisted of 10-12 weeks of treadmill running, 30 m/min, 60 min/day, 5 days/week (31, 43), while IST rats completed 10 weeks of IST consisting of six 2.5-min exercise bouts, with 4.5-min rest between bouts (60 m/min, 15% incline), 5 days/week (31). The Figure combines data from references (31, 32, 34, 35) for the effects of ET, (30, 31, 43) for IST and (36) for oxidative capacity.

accepted that a number of factors interact in a complex and to be established manner to promote pronounced increases in vascular conductance during exercise. The long list of mechanisms that are thought to contribute to exercise hyperemia is summarized on *Fig. 2*. Due to space limitations, we will focus on evidence concerning the effects of training on blood flow regulation. For an in depth discussion of mechanisms involved in exercise hyperemia the reader is referred to other reviews (49-52).

As emphasized above relative to structural adaptations, the understanding of how training affects vasomotor reactivity of skeletal muscle arteries requires acknowledgment that the importance of distinct control mechanisms varies significantly along the vascular network and is intrinsically related to muscle fiber type composition. For example, it is believed that small distal skeletal muscle arterioles may be more responsive to several vasoactive mediators than proximal large segments, possibly due to nonuniform expression of receptors and/or ion channels throughout the arteriolar tree (53, 54). Similarly, it has been suggested that both the release of metabolites during muscle contraction and the arteriolar responsiveness to metabolites might be different depending on

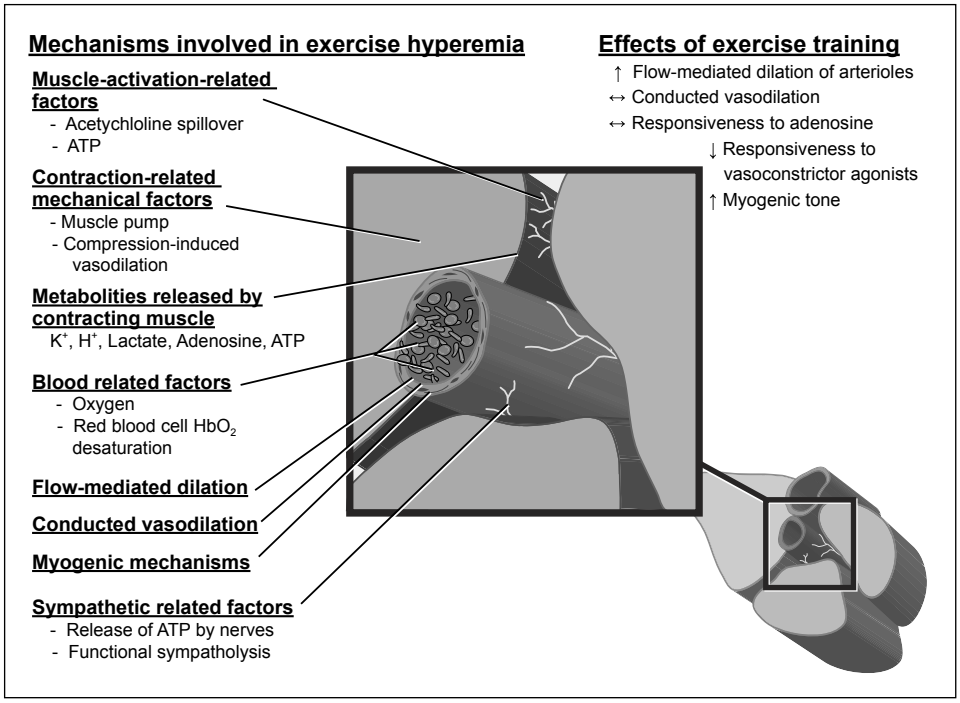

Fig. 2. Schematic representation of an arteriole surrounded by muscle fascicles. Mechanisms supposedly involved in causing exercise hyperemia are listed on the left and control processes believed to be altered in skeletal muscle vasculature by exercise training are summarized on the right. See text for details.

skeletal muscle fiber type composition (55, 56). In this scenario, it is expected that training induced-adaptations in the control of vascular conductance will occur non-uniformly within and between muscles depending on type and intensity of exercise.

VASCULAR ADAPTATIONS OF CONTROL OF CONDUCTANCE: ENDOTHELIUM

Endothelium dependent dilation (EDD) is the result of release of dilator substances (EDRF's) from the endothelium in response to various stimuli. Chemical signals activate phospholipase C (PLC) signaling increased intracellular free Ca^{2+} ($[Ca^{2+}]_I$), activating 3 processes: 1) phospholipase A_2 to release arachidonic acid (AA) which is converted to prostacyclin (PGI_2) by cyclooxygenase (COX); 2) eNOS to produce NO; and 3) release of unidentified endothelium derived hyperpolarizing factors (EDHFs) (57). Although it is clear that the endothelium plays a pivotal role in normal cardiovascular function (58-62), the contribution of EDRFs to exercise hyperemia appears to be modest (63-65). Nevertheless, there is substantial evidence indicating that exercise training can induce increases in EDD (5, 66-73).

We recently examined the effects of ET and IST on endothelium-dependent dilation and endothelial phenotype of arteries perfusing gastrocnemius and soleus muscles of rats (13, 14). Based on the proposition that the adaptations in the endothelium produced by exercise training result from changes in shear stress during exercise bouts (74-76) we hypothesized that exercise-induced vascular adaptations occur, spatially, in the area of muscle tissue with the greatest relative increase in fiber activity during exercise training bouts. Consistent with this hypothesis, we found that the distribution of training-induced adaptations in the arteries that perfuse gastrocnemius muscle were dramatically different following IST (13) and endurance training (14). After IST, acetylcholine-induced increases in blood flow were observed only in Gw muscle, while eNOS expression was increased non-uniformly in arteries perfusing both red and white gastrocnemius (13). In contrast, endurance trained rats exhibited increased acetylcholine-induced dilation in Gr and Gm but not in the soleus or Gw muscle and increased eNOS protein expression predominantly in vessels perfusing the red gastrocnemius (14). It should be emphasized that while increased eNOS expression was observed in the arterioles of the muscle tissue with the greatest relative increase in activity (Gr for ET and Gw for IST), not all arterioles in these tissues exhibited this adaptation (13, 14). Thus, IST did not uniformly increase expression of these proteins throughout the arteriolar tree perfusing the Gw muscle as our hypothesis predicted (13). In fact, increases in eNOS content were also seen in some Gr arterioles of IST rats. Whatever the exercise-induced signal for increased expression of eNOS (*e.g.* increased shear stress), these results suggest that this signal is not uniformly increased throughout the arteriolar tree perfusing the gastrocnemius muscle during ET or IST.

FLOW-INDUCED DILATION OF SKELETAL MUSCLE ARTERIOLES

A number of mechanisms supposedly involved in exercise hyperemia appear to have their vasodilatory effects mediated, at least partially, by endothelial derived NO (65), but evidence on the influence of training in these mechanisms is scarce. Among them, flow-mediated dilation of skeletal muscle resistance arterioles has received some attention and there is a growing amount of work in experimental animals demonstrating that exercise training increases arteriolar responsiveness to flow (73, 77-79). Noteworthy, as it is true for adaptations mentioned above, substantial heterogeneity seems to exist for training induced changes in responsiveness to flow within and between muscles. For example, in the rat gastrocnemuis, we observed that while second-order arterioles (2A) showed substantially increased dilatory responses to flow after ET, first-order arterioles dilated less when compared with the control group (14). Moreover, Jasperse and Laughlin (80) failed to find any significant difference in the responsiveness to flow after ET in the soleus muscle.

CONDUCTED VASODILATION

The dilatory response to muscle contraction is not uniform along the arteriolar tree, occurring faster and to a greater extent in the small arterioles (81). From distal remote sites, it is believed that dilation ascends to proximal larger segments, predominantly through endothelial cell-to-cell communication (53). Presumably, this mechanism is fundamental for the coordination of the dilatory response and given the velocity the signal travels, important for the early-onset dilatory response seen during contractions. Recently, Bearden *et al*. (82) tested the hypothesis that exercise training (voluntary running) for 8 weeks would increase the magnitude of the conducted response in second-order arterioles of the gluteus maximus muscle in mice. Unexpectedly, however, no differences were detected between groups for the maximal local and conducted responses to acetylcholine (82).

SUMMARY

In summary, exercise training induces nonuniform increase in EDD in the skeletal muscle vasculature. This effect appears to be more pronounced in the muscles recruited during exercise training, although considerable inhomogeneities can be seen even within the same vasculature. To this point, it is unknown the actual contribution of increased EDD to the observed increased BFC after ET and IST.

VASCULAR ADAPTATIONS OF CONTROL OF CONDUCTANCE: SMOOTH MUSCLE

Contrary to what is known for the endothelial cells, exercise-induced adaptations in vascular smooth muscle cells located in skeletal muscle

arteries/arterioles remain poorly understood. Being a pivotal player in regulating vascular resistance, it is likely that changes in vascular smooth muscle reactivity contribute to the observed increased blood flow capacity after exercise training. Furthermore, the recognition that factors such as cyclic stretch of the vessel wall, which is acutely altered during an exercise bout, can lead to pronounced modifications in VSMC phenotype (83), favors the notion that repeated exposures to physical activity might promote beneficial adaptations in the vascular smooth muscle (84). In this section we will address the modulatory effects of training on substances or factors that have their dilatory effects mediated, at least partially, by direct action on vascular smooth muscle cells.

ADENOSINE

Adenosine is released extracelluarly during muscle contraction and accumulates in the muscle interstitium in a parallel fashion with the muscle blood flow response (see Marshall (56) for review). The mechanisms of action on the vasculature are not entirely understood, but as suggested recently (56), A_{2A} receptors on the extra luminal surface of the arterial smooth muscle appear to have a predominant role for mediating the vasodilatory response to exercise (56). The contribution of adenosine to exercise hyperemia appears to be intensity-dependent (85), although a significant reduction in the steady-state blood flow during submaximal knee-extension exercise has been reported after adenosine blockade (86). Of special relevance, it has been suggested that spatial differences in adenosine release and responsiveness exist within and between muscles (87) and recent findings indicate that rather than controlling total flow, adenosine may contribute mainly to the regulation of blood flow heterogeneity (88).

Evidence regarding the modulatory effects of exercise training on vascular responsiveness to adenosine is scarce. Divergent findings have been reported in animal studies after treadmill training with studies showing reduced (89) or unaltered responsiveness (10) to adenosine in the gracilis and spinotrapezius muscles, respectively. Given that both muscles are not believed to be recruited during low to moderate running intensities in rats, caution must be used when interpreting these findings. McCurdy *et al*. reported that decreased physical activity (perhaps detraining) resulted in decreased sensitivity of isolated gastrocnemius arterioles to the dilator actions of adenosine (90) and did not alter responses of arterioles from soleus muscle. These results may suggest that exercise training will increase adenosine sensitivity in muscles known to be active during exercise.

ADRENERGIC VASOMOTOR REACTIVITY

Sympathetic activation during exercise is fundamental for the proper redistribution of blood flow toward active muscles (4). Equally important, the

notion that sympathetic removal or blockade (91, 92) increases muscle perfusion during both onset and sustained exercise, suggests that sympathetic activity is also elevated in exercising muscle and a competition between local dilatory factors and sympathetic-mediated vasoconstriction exists. In fact, the prevailing view remains that the vasculature within active muscle 'escapes' from sympathetic vasoconstriction, possibly through the release of vasoactive substances by the contracting muscle. Given the importance of sympathetic activation to muscle blood flow regulation during exercise, it is surprising that only a few studies have addressed the effects of training on vascular responsiveness to adrenergic stimuli. In humans, the limited evidence available seems to suggest that exercise training does not affect sympathetic-mediated constriction at rest (93, 94). A recent study also examined sympathetic vasoconstriction during moderate exercise in sedentary subjects and competitive cyclists and report no differences between groups (95).

In experimental animals, exercise training has been reported to alter reactivity of vascular smooth muscle to vasoconstrictor agonists in the abdominal aorta (66, 68, 79), as well as resistance arteries of the rat gastrocnemius muscle (13). Laughlin *et al*. (13) reported that IST decreased the vasoconstrictor responses of gastrocnemius feed arteries to phenylephrine but increased constrictor responses of Gw arterioles. Donato *et al*. (96) also reported that ET decreased the vasoconstrictor responses of gastrocnemius arterioles in old and young rats. In contrast to these observations in gastrocnemius arterioles, Jasperse *et al*. (80) reported that endurance exercise training did not alter the constrictor response of soleus feed arteries to phenylephrine. Similarly, Donato *et al*. (96) reported that exercise training did not alter vasoconstrictor responses of soleus arterioles of young rats but did decrease constrictor responses in soleus arterioles of old rats, a finding attributed to changes in the endothelium, not smooth muscle (96).

MYOGENIC RESPONSE

The state of contraction of vascular smooth muscle cells is modulated by changes in stretch produced by differences in transmural pressure (97). Following an increase in intravascular pressure, arterioles present a sustained level of contraction known as the myogenic response (98). It is currently unknown to what extent this response participates in exercise hyperemia, but it has been suggested that the mechanical compression of the vasculature evokes a dilatory response that has, in part, a myogenic origin (99, 100). To date, there is little information about the effects of exercise training on vascular reactivity to mechanical factors. In agreement with the hypothesis concerning the spatial distribution of adaptations in skeletal muscle, Laughlin *et al*. (13) reported that IST increased spontaneous tone in arterioles isolated from Gw but not arterioles from Gr in rats. Equally important, studies that have addressed the impact of inactivity induced by hindlimb unweighting on the myogenic response in rat skeletal muscle arterioles report heterogeneous adaptations depending on the muscle fiber type composition

surrounding the arteriole as well as a branch order effect. In 2A's isolated from the GW, Delp (101) found decreased myogenic responsiveness after hindlimb unloading, while Heaps and Bowles (102) found no effect in first-order arterioles. In the mixed gastrocnemuis, however, Heaps and Bowles found both increased spontaneous tone and myogenic responsiveness after ET (102).

CONCLUSIONS

In conclusion, available information indicates that training-induced increases in skeletal muscle BFC are the result of combinations of structural and functional vascular adaptations. Exercise training increases BFC through increases in capillarity, growth and remodeling of arterioles, alterations in endothelial and smooth muscle phenotypes and altered control of vascular resistance. Importantly, the relative contribution of each of these adaptations, and spatial distribution of the adaptations throughout the musculature are not uniformly distributed in the arteriolar network. Depending on the mode of training and the muscle fiber recruitment patterns associated with it, the duration and intensity of the training, these different mechanisms can all be activated to differing amounts to accomplish vascular adaptation. Thus, current results support the hypothesis that increases in BFC in skeletal muscle are the result of a mixture of increased arteriolar density, increased capillarity, and changes in control of resistance (30-32, 34, 35, 41).

In conclusion, as we entered into these experiments we conceived that the biologic strategy for vascular adaptation to training involved a mixture of angiogenesis of arteries, capillaries and veins and altered control of vascular resistance in skeletal muscle tissue undergoing adaptation. Our results indicate that fiber recruitment patterns during exercise and muscle fiber type composition interact with exercise intensity/duration to provide graded adaptations through each of these mechanisms within the arterial tree of skeletal muscle. In the light of these results it seems possible that each type of skeletal muscle (fast red, fast white, slow) can adapt *via* graded changes in capillarity, arteriolar density, and vascular control processes (4, 30-32, 34, 35, 42). Clearly more work is needed in this area because the biological strategies of the adaptations produced in response to altered activity in skeletal muscle of different phenotypes are only partially characterized at this time.

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