HIGHLIGHTED TOPIC | Skeletal and Cardiac Muscle Blood Flow

Integrative control of the skeletal muscle microcirculation in the maintenance of arterial pressure during exercise

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Delp, Michael D., and Donal S O’Leary. Integrative control of the skeletal muscle microcirculation in the maintenance of arterial pressure during exercise. J Appl Physiol 97: 1112–1118, 2004; 10.1152/japplphysiol.00147.2003.—Skeletal muscle blood flow and vascular conductance are influenced by numerous factors that can be divided into two general categories: central cardiovascular control mechanisms and local vascular control mechanisms. Central cardiovascular control mechanisms are thought to be designed primarily for the maintenance of arterial pressure and central cardiovascular homeostasis, whereas local vascular control mechanisms are thought to be designed primarily for the maintenance of muscle homeostasis. To support the high metabolic rates that can be generated during muscle contraction, skeletal muscle has a tremendous capacity to vasodilate and increase oxygen and nutrient delivery. During whole body dynamic exercise at maximal oxygen consumption (V˙O₂ max), the skeletal muscle receives 85–90% of cardiac output. Yet despite receiving such a large fraction of cardiac output during high-intensity exercise, a vasodilator reserve remains with the potential to produce further elevations in skeletal muscle vascular conductance and blood flow. However, because maximal cardiac output is reached during exercise at V˙O₂ max, further elevations in muscle vascular conductance would produce a fall in arterial pressure. Therefore, limits on muscle perfusion must be imposed during whole body exercise to prevent such drops in pressure. Effective arterial pressure control in response to a potentially hypotensive challenge during high-intensity exercise occurs primarily through reflex-mediated increases in sympathetic nerve activity, which are capable of modulating vasomotor tone of the skeletal muscle resistance vasculature. Thus skeletal muscle vascular conductance and perfusion are primarily mediated by local factors at rest and during exercise, but other centrally mediated control systems are superimposed on the dominant local control mechanisms to provide an integrated regulation of both arterial pressure and skeletal muscle vascular conductance and perfusion during whole body dynamic exercise.

maximal exercise; blood pressure; vascular resistance; sympatholysis; vasoconstriction; muscle sympathetic nerve activity

THE CARDIOVASCULAR SYSTEM must respond to a variety of physical stresses, including gravitational stress during orthostasis, hypoxia, thermal stress, and exercise, to maintain the appropriate match between tissue metabolism and perfusion. Quite often, however, there are competing local demands for blood flow that challenge the balance between cardiac output (Q˙) and total vascular conductance in the maintenance of arterial pressure. This is certainly true during high-intensity dynamic exercise, where the capacity of the active skeletal muscle to vasodilate and increase vascular conductance is considerable. The purpose of this review is to briefly highlight some of the mechanisms believed to be responsible for regulating skeletal muscle blood flow and vascular conductance during dynamic steady-state exercise and outline how central control and local control of muscle vascular conductance are integrated in the maintenance of arterial pressure during exercise.

At rest, skeletal muscle receives ~20% Q˙ in humans (42). In animals, where the skeletal muscle mass makes up a similar fraction of the body mass as in humans, skeletal muscle receives ~40% Q˙ when the animals are standing and awaiting a bout of exercise (3). This presumably is an overestimate of the amount of Q˙ going to muscle at “rest.” During submaximal exercise performed at 70% of maximal oxygen uptake (V˙O₂ max), the proportion of Q˙ going to muscle increases to ~80% Q˙ (Fig. 1) (3). During exercise performed at V˙O₂ max, direct measures of Q˙ distribution with microspheres in miniature pigs (3, 34) and dogs (33) and estimates of Q˙ distribution...
ever, because maximal $Q$ ($Q_{\text{max}}$) is reached during exercise at $V_{O_2\text{max}}$, further elevations in muscle vascular conductance would have to be matched by decreases in vascular conductance in other tissues to maintain arterial pressure. As is evident from Fig. 1, the low flows at $V_{O_2\text{max}}$ to skin, fat, bone, and renal and splanchnic tissues prevents further diversion of blood away from these tissues (3, 34, 35). Thus experimental exploitation of the skeletal muscle vasodilator reserve to increase muscle blood flow during exercise at $V_{O_2\text{max}}$, when $Q_{\text{max}}$ is achieved and the ability to further reduce perfusion of inactive tissue is limited, produces both a modest increase in $V_{O_2\text{max}}$ and a fall in arterial pressure (26). These studies demonstrate that limitations on vascular conductance are normally imposed in the skeletal muscle during submaximal, maximal, and supramaximal whole body exercise in miniature swine to prevent drops in arterial pressure.

Conclusions regarding imposed limits on skeletal muscle vasodilation are not unique to quadrupeds (43, 45). For example, blood flow to human knee extensors increases as a function of exercise intensity to a peak of $\sim$225 ml·min$^{-1}$·100 g$^{-1}$ without indication of plateau when the active mass is small and does not tax the pumping capacity of the heart (2). However, whole body exercise engages a much larger fraction of the total muscle mass, which in humans, miniature pigs, rats and mice constitutes 35–40% of body mass (3, 6). Therefore, if one assumes that only one-half the total muscle mass of a 70-kg individual is active during maximal whole body exercise (i.e., 14 kg active muscle), then this level of perfusion would require that 31.5 l/min of $Q_{\text{max}}$ be directed to the active skeletal muscle, in addition to the perfusion requirements of the heart, brain, and other tissues. Such high muscle blood flows would be unattainable during whole body exercise for most humans.

Fig. 1. Distribution of cardiac output to various body compartments in miniature swine at rest and during exercise at submaximal (70% maximal $O_2$ consumption [$V_{O_2\text{max}}$]), maximal (100% $V_{O_2\text{max}}$), and supramaximal ($\sim$115% $V_{O_2\text{max}}$, based on extrapolation of the $O_2$ consumption-exercise intensity relation) intensities. [Adapted from data published by Armstrong and colleagues (3, 34).]

Increases in blood flow and vascular conductance do not occur uniformly in muscle but are related to muscle fiber type, oxidative capacity, and patterns of muscle fiber recruitment (3, 10, 25). In going from rest to exercise at 70% $V_{O_2\text{max}}$, blood flow and vascular conductance increase primarily in muscles composed of slow-twitch oxidative (type I) and fast-twitch oxidative (type IIA) fibers (Fig. 2). A further increase in exercise intensity to that eliciting $V_{O_2\text{max}}$ results in elevations in vascular conductance in muscle composed predominantly of fast-twitch oxidative and fast-twitch glycolytic (type IIB) fibers, whereas vascular conductance in slow-twitch muscle remains unchanged (Fig. 2). $Q$ and muscle vascular conductance attained during exercise at $V_{O_2\text{max}}$ represent peak values during whole body dynamic exercise, since further increases in exercise intensity and muscle work to supramaximal levels ($\sim$115% $V_{O_2\text{max}}$) do not evoke further elevations in $Q$ or muscle vascular conductance (Figs. 1 and 2). Only cardiac muscle blood flow and vascular conductance continue to increase during exercise beyond $V_{O_2\text{max}}$ (34).

Although peak vascular conductance is attained during submaximal and maximal exercise in slow-twitch and fast-twitch muscle, respectively, a vasodilator reserve still exists in respiratory and locomotor muscles, regardless of muscle fiber composition, which could accommodate greater elevations in vascular conductance than those occurring at $V_{O_2\text{max}}$ (26). However, because maximal $Q$ ($Q_{\text{max}}$) is reached during exercise at $V_{O_2\text{max}}$, further elevations in muscle vascular conductance would have to be matched by decreases in vascular conductance in other tissues to maintain arterial pressure. As is evident from Fig. 1, the low flows at $V_{O_2\text{max}}$ to skin, fat, bone, and renal and splanchnic tissues prevents further diversion of blood away from these tissues (3, 34, 35). Thus experimental exploitation of the skeletal muscle vasodilator reserve to increase muscle blood flow during exercise at $V_{O_2\text{max}}$, when $Q_{\text{max}}$ is achieved and the ability to further reduce perfusion of inactive tissue is limited, produces both a modest increase in $V_{O_2\text{max}}$ and a fall in arterial pressure (26). These studies demonstrate that limitations on vascular conductance are normally imposed in the skeletal muscle during submaximal, maximal, and supramaximal whole body exercise in miniature swine to prevent drops in arterial pressure.

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Fig. 2. Vascular conductance at rest and during exercise at submaximal, maximal, and supramaximal intensities in the medial head of the triceps brachii muscle (TBM), composed primarily of slow-twitch oxidative fibers, the deep portion of the long head of the triceps brachii muscle (TBL$\text{deep}$), composed primarily of fast-twitch oxidative fibers, and the superficial portion of the long head of the triceps brachii muscle (TBL$\text{superf}$), composed primarily of fast-twitch glycolytic fibers (3). Values were derived from the original miniature swine blood flow and arterial pressure data published by Laughlin, Armstrong, and colleagues (26, 34). Values are means $\pm$ SE. *Mean different from standing mean; $^\dagger$mean different from 70% $V_{O_2\text{max}}$ mean ($P < 0.05$).
because this perfusion rate exceeds $Q_{\text{max}}$ except in some endurance-trained athletes (13). However, even in these individuals, it is doubtful that a large proportion of the muscle attains a perfusion rate of this magnitude because the assumption that only one-half of the total muscle mass is active and increases perfusion during whole body dynamic exercise is an underestimate, based on animal studies demonstrating that virtually all respiratory and locomotor muscles increase blood flow to varying degrees during high-intensity exercise (3, 4, 32, 33). Most likely, perfusion rates of 225 ml·min$^{-1}$·100 g$^{-1}$ or higher are limited in humans to the most highly oxidative muscles during dynamic whole body exercise (3, 4, 10), which in rats make up $\sim$25–30% of the total muscle mass (10). Therefore, because the capacity of the muscle to elevate vascular conductance far surpasses the capacity of the heart to elevate $Q_{\text{max}}$, limits on muscle perfusion must be imposed during whole body exercise to prevent drops in arterial pressure and, consequently, cerebral perfusion.

Given the capacity of the skeletal muscle to increase vascular conductance and its vasodilator reserve during whole body dynamic exercise, effective arterial pressure control in response to a potentially hypotensive challenge during high-intensity exercise could only occur via a central cardiovascular control mechanism capable of modulating vasomotor tone of the skeletal muscle resistance vasculature (19, 26, 35). However, the ability to elicit vasoconstriction within active skeletal muscle is somewhat controversial. In 1962, Remensnyder et al. (41) concluded that active skeletal muscles respond weakly to sympathetic activation, termed functional sympatholysis. Subsequent studies both support (e.g., Refs. 7, 20, 23, 24, 53, 54, 55) and refute (e.g., Refs. 8, 12, 21, 36, 48, 50, 51, 52) this conclusion. To some extent, however, this conclusion may be dependent on the method of data analysis (35).

Blood flow may vary with changes in both perfusion pressure and vasomotor tone; thus blood flow by itself cannot be used as a reliable index of vascular responses. Rather, vascular resistance (perfusion pressure/flow) or vascular conductance (flow/perfusion pressure) is used to detect changes in blood vessel caliber. These two reciprocally related indexes are often thought of as interchangeable because increases in resistance correspond to decreases in conductance and vice versa. However, a reciprocal relation is highly nonlinear, and, with large changes in the baseline level of skeletal muscle blood flow during rest and exercise, opposite conclusions can be reached when using resistance vs. conductance to quantify the magnitude of a vasoconstrictor response. Figure 3 shows a theoretical experiment in which a 50% decrease in blood flow occurs in skeletal muscle at rest and during exercise (for simplicity, perfusion pressure remains constant at 1 unit). At rest, this vasoconstriction results in a small absolute decrease in conductance (from its low baseline level) and a large absolute increase in resistance (from its large baseline level). During exercise, blood flow and vascular conductance increase markedly and resistance falls to a low level. In this setting, the same 50% reduction in flow yields a large decrease in conductance and a miniscule increase in resistance. Thus, in terms of the absolute changes in conductance, a larger vasoconstriction occurred during exercise whereas, in terms of resistance, the response at rest was much greater than that during exercise. Because vasoconstriction cannot be both larger and smaller at the same time, then either vascular resistance or conductance would appear to more accurately reflect the vasoconstrictor response of the vasculature but not both. To confound matters even more, vasoconstriction analyzed on a relative basis, i.e., a percent change, results in identical responses: a 50% decrease in conductance occurring at rest and during exercise and a 100% increase in resistance occurring in both conditions. Thus the three most common forms of data analyses yield three distinct conclusions: 1) a larger vasoconstriction occurring during exercise vs. rest using conductance, 2) a smaller vasoconstriction occurring during exercise vs. rest using resistance, and 3) exactly the same vasoconstriction occurring during rest and exercise using a percent change in either resistance or conductance. Therefore, conclusions regarding the state of the skeletal muscle vascular bed during exercise are highly dependent on the method of data analysis.

![Figure 3](https://example.com/figure3.png)

**Fig. 3.** Results from a theoretical experiment when a 50% decrease in blood flow occurs in skeletal muscle at rest and during strenuous dynamic exercise (perfusion pressure remains constant at 1 unit for simplicity). At rest, this vasoconstriction (VC at arrows) causes a small decrease in conductance but a large increase in resistance. The reverse occurs during exercise, i.e., a large decrease in conductance but a small increase in resistance [changes ($\Delta$) during low- and high-flow states shown on right]. Therefore, opposite conclusions would be reached when one uses conductance vs. resistance to quantify the effect of exercise on the magnitude of the vasoconstrictor response. This issue is further confounded because the percent change for each index is exactly the same at rest and exercise (see text for details).
vasoconstriction are markedly dependent on how one defines "vasomotor strain," and the quandary of exactly which index of the vasoconstrictor response best reflects "vasoconstriction" remains. This can become a circular argument.

Recently, Collins et al. (8) took a different approach to address this problem. Rather than argue the merits of using one index over another, they directly calculated the importance of the vasoconstriction in skeletal muscle in mediating a baroreflex-induced pressor response (elicited via bilateral carotid occlusion). This was possible because Q and hindlimb skeletal muscle blood flow were measured simultaneously, along with arterial and central venous pressures (and renal flow as well). Collins et al. found in dogs running on a treadmill that, as exercise intensity increased, more and more of the \( \sim 35 \text{ mmHg} \) baroreflex-induced increase in arterial pressure was due to vasoconstriction in skeletal muscles and progressively less was due to renal vasoconstriction. Importantly, these conclusions are independent of whether resistance or conductance is used for the calculations (although the equations are simpler when conductance is used). These authors concluded that, as workload increases, vasoconstriction within skeletal muscle became progressively more important in mediating the baroreflex pressor response. However, what remains unknown is whether this occurs via the same baroreflex-induced increase in sympathetic tone or whether for a given hypotensive challenge the baroreflex elicits greater increases in sympathetic activity to the skeletal muscles as exercise intensity increases. Should the latter be true, then this could rectify the disparate conclusions regarding the existence of sympatholysis. In other words, modest reductions in the efficacy of given increases in sympathetic activity could occur in active skeletal muscle, but this would be offset by larger rises in sympathetic tone for a given hypotensive stimulus. Thus skeletal muscle can become the most important target organ for baroreflex responses to hypotensive challenges, but greater increases in sympathetic activity may be required to accomplish effective vasoconstriction during exercise, regardless of how vasoconstriction is defined.

MECHANISMS TO ELEVATE SYMPATHETIC NERVE ACTIVITY DURING EXERCISE

The origins of the increase in sympathetic activity with exercise are not firmly established but likely involve the action of and interaction among at least three separate systems: 1) central command, 2) the arterial baroreflex, and 3) reflex responses to activation of mechanosensitive and metabosensitive afferents within the active skeletal muscle (30, 42–44). Central command refers to reflex changes in autonomic outflow accompanying the volition to exercise. It is thought that activation of motor systems causes parallel stimulation of brain stem cardiovascular regulatory centers, which cause changes in autonomic nerve activity. This is a positive, feedforward reflex in contrast to a negative, feedback reflex, such as the arterial baroreflex. For many years, it was thought that the arterial baroreflex must be turned off during exercise inasmuch as both heart rate and arterial pressure increase. However, several studies have now shown that the arterial baroreflex is reset to a higher pressure during exercise (8, 38, 52). Thus, rather than opposing the increases in sympathetic tone during exercise, the arterial baroreflex may participate in this increase in an attempt to raise arterial pressure to a higher baroreflex set point. What causes this resetting is uncertain, but both central command and activation of skeletal muscle afferents have been implicated (29). Skeletal muscle contains group III and IV fibers, which are sensitive to increases in tension as well as to increases in the interstitial concentration of chemicals released during increased metabolic activity (30). Activation of these afferents can cause large increases in sympathetic output, arterial pressure, heart rate, and Q (44). To what extent each of these systems participates in the regulation of sympathetic outflow during exercise is not well established and likely differs with different modes of exercise as well as with different exercise intensities. For example, metabosensitive skeletal muscle afferents are not likely active during mild dynamic exercise. In contrast, the rapid initial tachycardia at the onset of exercise is likely due to activation of central command causing rapid, partial inhibition of parasympathetic activity and some activation of sympathetic tone (44).

In addition to the traditional concept of central command, baroreflexes, and muscle reflexes activating the sympathetic nervous system during exercise, two other mechanisms have been identified that may also contribute to sympathetic outflow during exercise. The first is activation of the otolith organs and vestibular system, which has been shown to increase muscle sympathetic nerve activity and elicit vasoconstriction of the skeletal muscle of the forearm and calf (22, 31, 49). In support of this notion is a report demonstrating that the perfusion and prescriptive activity of the vestibular nuclei increase during exercise and as a function of exercise intensity in the miniature swine (9). Because locomotion (e.g., running) stimulates the otolith organs, it is reasonable to assume that this mechanism contributes to the overall sympathetic discharge during exercise. A second possible mechanism of activation is through heat generation, a major product of muscle contraction and exercise. Studies have demonstrated that elevated muscle temperature, as would be observed during exercise, increases muscle sympathetic outflow during forearm exercise (39). Conversely, a decrease in muscle temperature has been shown to decrease muscle sympathetic nerve activity during forearm exercise (40). Thus vestibular and thermal reflexes may contribute to the neural control of arterial pressure and blood flow distribution during exercise.

LOCAL MECHANISMS OF VASCULAR REGULATION AND SYMPATHOLYSIS

Skeletal muscle blood flow and vascular conductance are influenced by numerous factors that can be divided into two general categories: central cardiovascular control mechanisms and local vascular control mechanisms. As indicated above, central cardiovascular control mechanisms are thought to be designed primarily for the maintenance of arterial pressure and central cardiovascular homeostasis, whereas local vascular control mechanisms are thought to be designed primarily for the maintenance of tissue homeostasis (42). In skeletal muscle, local vascular control mechanisms involved in exercise hyperemia include metabolic factors, endothelium-mediated regulation, propagated responses, myogenic control, and the muscle pump (compare Refs. 11, 27). The prevailing view is that muscle perfusion and vascular conductance are primarily mediated by local factors at rest and during exercise and that other control systems are superimposed on the dominant local con-
control mechanisms (11, 27). For example, removal of sympathetic neural influences through acute lumbar sympathectomy increases rat hindlimb blood flow during low-intensity exercise (37), demonstrating the competition that exists between sympathetic vasoconstriction and local vasodilator factors during submaximal exercise.

The preponderance of evidence indicates that the primary determinant of skeletal muscle perfusion during steady-state exercise is the metabolic rate of the muscle (compare Refs. 18, 27). According to the metabolic theory of blood flow control, tissue metabolism and arteriolar smooth muscle constitute a local control system that couples oxygen and nutrient delivery with tissue metabolism. In this system, increases in muscle metabolism, such as occurs during exercise, alter release of vasoactive substances (e.g., decreased PO$_2$ and pH and increased Pco$_2$, osmolarity, adenosine, adenosine nucleotides, potassium, histamine, kinines, phosphates, nitric oxide, and prostaglandins), which diffuse into the interstitial fluid surrounding resistance arterioles. Relaxation of vascular smooth muscle through the direct and propagated action of metabolites causes vasodilation of proximal arterioles and feed arteries that result in elevations in muscle blood flow, whereas vasodilation of terminal arterioles increases capillary recruitment (15, 17, 47). Indeed, capillaries physically located in close proximity to active muscle fibers are capable of sensing a variety of metabolically and neurally associated signaling molecules and transmitting vasodilator or vasoconstrictor signals to upstream terminal arterioles to increase or decrease perfusion of discrete capillary networks (5, 46). The increased oxygen delivery that results from metabolic vasodilation brings oxygen supply into equilibrium with muscle oxygen demand, and this appears to be spatially coupled to patterns of muscle fiber recruitment (16, 46). Thus the metabolic hypothesis predicts that oxygen delivery to muscle, not blood flow per se, is the locally controlled variable that sustains the exercise hyperemia.

In addition to the direct action of metabolites to induce smooth muscle relaxation, metabolic vasodilators also appear to compete with sympathetically mediated vascular tone (41, 56). The original concept of functional sympatholysis referred to local control factors overriding sympathetic vasoconstriction by making vascular smooth muscle less sensitive to catecholamines (i.e., postjunctional inhibition) (24, 41). Studies indicate that there is a differential sensitivity of $\alpha_1$- and $\alpha_2$-adrenergic vasoconstriction to metabolic vasodilation produced during skeletal muscle contraction. Anderson and Faber (1) reported that metabolic vasodilator substances produce 10 times greater opposition to $\alpha_2$-mediated vasoconstriction than to constriction mediated by $\alpha_1$-receptors. Furthermore, the heterogeneous distribution of postjunctional $\alpha_1$- and $\alpha_2$-adrenoceptors within the microcirculation of rat cremaster muscle [large resistance arterioles possessing both $\alpha$-receptor subtypes and small terminal arterioles possessing a predominance of $\alpha_2$-receptors (14)] suggests that low-intensity exercise may preferentially affect $\alpha_2$-mediated vasoconstriction of terminal arterioles, thereby increasing capillary recruitment. As exercise intensity increases and metabolite concentration becomes greater (28), inhibition of both $\alpha$-receptor subtypes in the proximal resistance arteries may then preferentially increase the magnitude of muscle blood flow. This conjecture is, however, based on the assumption that the distribution of $\alpha$-receptor subtypes within the cremaster muscle vasculature reflects that within the vasculature of locomotor muscles. It is unlikely that vascular control mechanisms operative in the cremaster muscle, a nonlocomotor striated muscle with no skeletal attachments, are the same as those of locomotory skeletal muscles. For example, Thomas et al. (54) reported that the relative importance of $\alpha_1$- and $\alpha_2$-adrenergic vasoconstriction during exercise differs between oxidative and glycolytic muscles. Although these data do not necessarily confirm that $\alpha$-receptor subtype distribution varies among muscles, they do reveal that adrenergic vascular control mechanisms can be distinct among muscles with varying fiber compositions and oxidative capacities.

In addition to the concept of postsynaptic inhibition of sympathetic vasoconstriction, an alternative view also holds that release of norepinephrine from sympathetic adrenergic nerve endings within the wall of resistance arteries is inhibited by certain metabolites (i.e., prejunctional inhibition) (42, 56). Thus, from the work of Remensnyder et al. (41) and Kjellmer (24), the notion emerged that sympathetic nerve activity increases during exercise to all tissues, functioning to decrease vascular conductance in visceral tissue, skin, and inactive skeletal muscle. At the same time, increases in vascular conductance and blood flow are made possible in contracting skeletal muscle through prejunctional and postjunctional sympatholytic mechanisms (although, as discussed above, data analysis may potentially confound these conclusions). The decreased forearm muscle blood flow observed with leg exercise (20) and the simultaneous increased blood flow to high oxidative portions of muscle and decreased blood flow to low oxidative portions of the same muscle observed during low-intensity exercise (3, 25) are several studies among others (e.g., Refs. 7, 20, 23, 24, 26, 34, 53–55) supporting the concept that functional sympatholysis enables active muscles to increase blood flow and vascular conductance despite elevations in muscle sympathetic nerve activity. However, the inhibition of sympathetically mediated vascular tone is not complete during submaximal or maximal exercise (23, 26, 34, 37). Limits on skeletal muscle vascular conductance are imposed through reflex-mediated increases in sympathetic activity to prevent drops in arterial pressure during high-intensity dynamic exercise.

**FUTURE DIRECTIONS**

Our understanding of the cardiovascular response to exercise and the integration of central cardiovascular and local control mechanisms to maintain arterial pressure and tissue homeostasis have advanced tremendously in the past 40 years. However, much about the basic integration of neural and vascular mechanisms remains to be discovered, and much remains to be learned regarding how cardiovascular reflex and local vascular control mechanisms adapt or are altered with exercise training, deconditioning, microgravity, aging, and a host of pathological conditions. Integrative experimental approaches from molecular technologies to in vitro and in vivo experimentation provide
great promise for those aspiring to expand our understanding of cardiovascular responses to exercise.

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REFERENCES


