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Adrenergic and non-adrenergic control of active skeletal muscle blood flow: Implications for blood pressure regulation during exercise

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ABSTRACT

Blood flow to active skeletal muscle increases markedly during dynamic exercise. However, despite the massive capacity of skeletal muscle vasculature to dilate, arterial blood pressure is well maintained. Sympathetic nerve activity is elevated with increased intensity of dynamic exercise, and is essential for redistribution of cardiac output to active skeletal muscle and maintenance of arterial blood pressure. In addition, aside from the sympathetic nervous system, evidence from human studies is now emerging that supports roles for non-adrenergic vasoconstrictor pathways that become active during exercise and contribute to vasoconstriction in active skeletal muscle. Neuropeptide Y and adenosine triphosphate are neurotransmitters that are co-released with norepinephrine from sympathetic nerve terminals capable of producing vasoconstriction. Likewise, plasma concentrations of arginine vasopressin, angiotensin II (Ang II) and endothelin-1 (ET-1) increase during dynamic exercise, particularly at higher intensities. Ang II and ET-1 have both been shown to be important vasoconstrictor pathways for restraint of blood flow in active skeletal muscle and the maintenance of arterial blood pressure during exercise. Indeed, although both adrenergic and non-adrenergic vasoconstriction can be attenuated in exercising muscle with greater intensity of exercise, with the higher volume of blood flow, the active skeletal muscle vasculature remains capable of contributing importantly to the maintenance of blood pressure. In this brief review we provide an update on skeletal muscle blood flow regulation during exercise with an emphasis on adrenergic and non-adrenergic vasoconstrictor pathways and their potential capacity to offset vasodilation and aid in the regulation of blood pressure.

1. Introduction

Profound cardiovascular adjustments occur during dynamic exercise to match oxygen supply to the metabolic needs of active skeletal muscle. The requisite increase in blood flow to active skeletal muscle requires up to a fivefold increase in cardiac output in combination with substantial increases in vascular conductance within the exercising muscles. Increases in heart rate, cardiac contractility, and venous return all contribute to the elevations in cardiac output. Decreased vascular conductance in non-active tissue and increased vascular conductance in active skeletal muscle become essential for the redistribution of cardiac output to active skeletal muscle. Compared to resting values of ~15% of cardiac output, active skeletal muscle can receive upwards of ~85% of cardiac output during maximal exercise (Buckwalter and Clifford, 2001). Indeed, during high intensity dynamic exercise, active skeletal muscle blood flow can increase nearly 100-fold over resting values (Laughlin et al., 2012; Segal, 2005). However, if left unchecked, this massive capacity of skeletal muscle vasculature to dilate could impose a challenge to the maintenance of arterial blood pressure. In this brief review we provide an update on skeletal muscle blood flow regulation during exercise with an emphasis on vasoconstrictor pathways and their potential capacity to offset vasodilation and aid in the regulation of blood pressure. This review was designed to focus primarily on recently published studies in healthy humans with only brief mention of animal studies when applicable. We also site additional review articles throughout to direct the reader to further work in these important areas.

2. Modulation of skeletal muscle blood flow

Investigations of mechanical and metabolic control mechanisms responsible for the vast increases in blood flow to active skeletal muscle have been conducted since the late 19th century (Rowell, 2004). Exercise hyperemia is the result of a multifaceted interaction that includes the mechanical effects of muscle contraction and the complex interplay between numerous vasoactive compounds, the relative contribution of which can vary over the time course of an exercise bout. The rapid rise in blood flow following the onset of muscle contraction (within 1 s) has been attributed to the mechanical interaction between contracting

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skeletal muscle and the vasculature (i.e., the muscle pump) (Laughlin, 1987). Muscle contraction can partly facilitate perfusion via a pumping effect on the venous circulation. In addition, dilation of skeletal muscle feed arteries in response to extravascular compression may also contribute to the initial increase in blood flow following muscle contraction (Clifford et al., 2006), although findings are inconsistent (Sheriff et al., 1993). Identification of a metabolic by-product that participates in the initiation of exercise hyperemia has proven to be challenging, in part, due to the rapid and robust rise in muscle blood flow. Indeed, at the onset of single leg kicking, femoral artery blood flow can increase up to 5-fold within 5 s at a peak exercise intensity (Radegran and Saltin, 1998) (Fig. 1). Although this latency has been suggested to be too soon to be accounted for by metabolic processes, there is support for a role of potassium in the early stages of the hyperemic response. With a single 5-s contraction of the human quadriceps muscle, femoral venous blood concentrations of potassium have been shown to increase and peak within 5 s after the end of contraction (Kiens et al., 1989) with similar findings in animal studies (Mohrman and Sparks, 1974). In an effort to focus on the rapidity of the blood flow responses to exercise, studies have been performed using single 1-s muscle contractions to assess the ensuing rapid onset vasodilation. These studies have consistently demonstrated a clear and rather large intensity dependent increase in muscle blood flow initiated by a brief muscle contraction, which peaks within ~5 s. This rapid onset, monophasic dilation following a single muscle contraction has been expertly reviewed, highlighting the potential contributions of mechanical compression of the vasculature and proposed vasodilator systems (Clifford, 2007). Notably, recent work by Crecelius et al. (2013) identified a role for potassium mediated hyperpolarization in combination with nitric oxide and prostaglandins in mediating contraction induced rapid onset vasodilation.

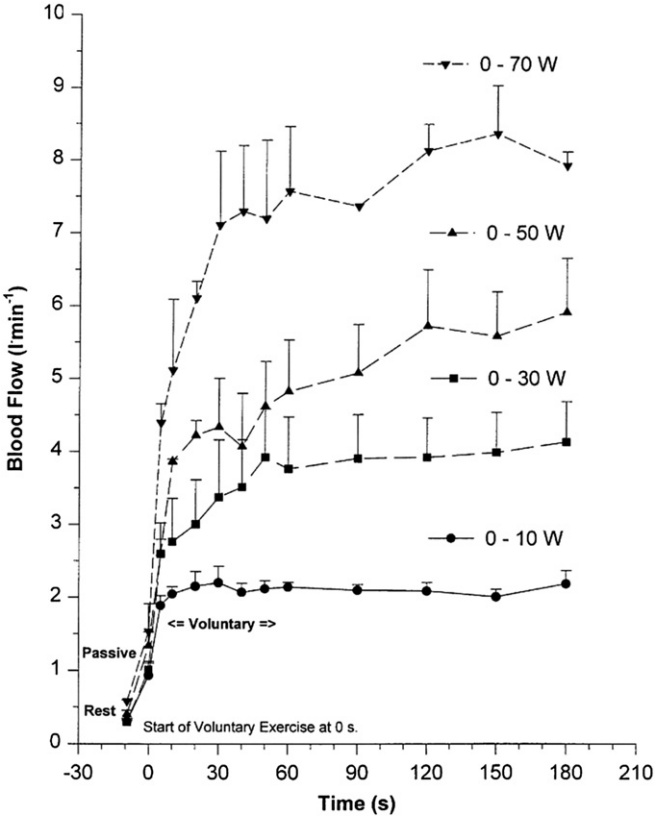

Fig. 1. Continuously measured femoral artery blood flow (Doppler ultrasound) at rest, during passive movement of the knee-extensor muscle group, and at onset of voluntary single leg knee extension exercise up to steady-state performed at different power outputs. Reproduced with permission from Radegran and Saltin (1998).

The mechanism(s) responsible for the initial onset of exercise hyperemia may be different than those that maintain it because of the changing metabolic demand and local milieu of vasodilator compounds over the time course of exercise. The maintenance of skeletal muscle blood flow during steady-state dynamic exercise largely depends on the metabolic influences on arteriolar smooth muscle. Extensive research has revealed the role of a number of vasodilator-promoting factors produced by active skeletal muscle, such as adenosine, potassium, histamine, phosphates, prostaglandins, nitric oxide (NO), endothelium-derived hyperpolarizing factor, increases in osmolarity and PCO_2, and decreases in PO_2 and pH (Clifford and Hellsten, 2004; Hellsten et al., 2012; Joyner and Wilkins, 2007; Laughlin et al., 2012; Saltin et al., 1998; Segal, 2005). A redundant interaction between these vasodilatory systems appears to exist, such that one vasoactive compound may take over when the formation of another is compromised. For example, nitric oxide synthase (NOS) inhibition in the leg reduces femoral artery blood flow by ~50% at rest and ~35% during recovery of exercise, but has minimal effect during dynamic single leg exercise (Radegran and Saltin, 1999). However, significant reductions in femoral artery blood flow during dynamic single leg exercise have been reported with combined NOS and prostaglandin inhibition (Mortensen et al., 2007). The redundant effects of these vasodilator compounds may also be dependent on the experimental model. In contrast to the leg, local NOS inhibition with L-NMMA in the exercising forearm reduces blood flow by ~20%, which is unaffected by prostaglandin synthesis inhibition (Schrage et al., 2004). Together, these findings and others highlight the complex interaction and redundancy among vasodilator systems, and a general consensus has been established that no single vasodilatory compound can account for exercise hyperemia (Clifford and Hellsten, 2004; Hellsten et al., 2012; Joyner and Wilkins, 2007; Laughlin et al., 2012; Saltin et al., 1998; Segal, 2005). However, emerging evidence points to similar mechanisms being active at the onset and during steady-state exercise with a major role for potassium (Crecelius et al., 2014).

Although increases in active skeletal muscle blood flow are an essential component of the cardiovascular adjustments to exercise, it is also clear that exercise hyperemia must also be met with restraint to defend against hypotension, particularly when the mass of active muscle is large (Calbet et al., 2004; Saltin, 2007). Indeed, without restraint, active skeletal muscle blood flow can rise disproportionately even during mild intensity dynamic exercise (Sheriff et al., 1993). Given the robust potential vasodilation in skeletal muscle and the upper limit of cardiac output, a lack of restraint clearly puts maintenance of blood pressure in jeopardy. Herein, we will attempt to bring together the vasoconstrictor pathways that are in play during dynamic exercise to modulate vasodilatory responses and support blood pressure, including the more recently investigated non-adrenergic vasoconstrictor pathways (see Fig. 2).

3. Sympathetic control of blood flow to active skeletal muscle

Norepinephrine is the predominant neurotransmitter released from sympathetic nerve terminals. Upon release, norepinephrine can bind to α_1- or α_2-adrenergic receptors on vascular smooth muscle to cause vasoconstriction, and can also act on α_2-adrenergic receptors on presynaptic sympathetic nerve terminals to inhibit neurotransmitter release. Early studies measuring plasma norepinephrine as an estimation of sympathetic nerve activity observed elevations beginning at moderate levels of dynamic exercise and subsequently increasing markedly in a work load-dependent manner up to maximal intensity (Christensen and Galbo, 1983; Seals, 2006). Similar observations have been made from studies using the norepinephrine spillover technique (Esler et al., 1990; Savard et al., 1989). Interestingly, Savard et al. (1989) measured norepinephrine spillover from both active and inactive limbs during one legged knee extensor exercise and demonstrated significantly greater increases in the exercising limb. Studies using microneurography for direct measures of muscle sympathetic nerve activity (MSNA) have shown graded