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Changes in the control of skin blood flow with exercise training: where do cutaneous vascular adaptations fit in?

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Abstract

Heat is the most abundant byproduct of cellular metabolism. As such, dynamic exercise in which a significant percentage of muscle mass is engaged generates thermoregulatory demands that are met in part by increases in skin blood flow. Increased skin blood flow during exercise adds to the demands on cardiac output and confers additional circulatory strain beyond that associated with perfusion of active muscle alone. Endurance exercise training results in a number of physiological adaptations which ultimately reduce circulatory strain and shift thermoregulatory control of skin blood flow to higher levels of blood flow for a given core temperature. In addition, exercise training induces peripheral vascular adaptations within the cutaneous microvasculature indicative of enhanced endothelium-dependent vasomotor function. However, it is not currently clear how (or if) these local vascular adaptations contribute to the beneficial changes in thermoregulatory control of skin blood flow following exercise training. The purpose of this Hot Topic review is to synthesize the literature pertaining to exercise training-mediated changes in cutaneous microvascular reactivity and thermoregulatory control of skin blood flow. In addition, we address mechanisms driving changes in cutaneous microvascular reactivity and thermoregulatory control of skin blood flow, and pose the question: what (if any) is the functional role of increased cutaneous microvascular reactivity following exercise training?

Keywords

exercise training; physical activity; vascular adaptations; skin

Introduction

Control of blood flow to the non-acral (hairy) skin is accomplished via two branches of the sympathetic nervous system: an adrenergic vasoconstrictor system and a cholinergic vasodilator system (Kellogg, 2006). Passive thermal stress results in reflex adjustments that decrease vasoconstrictor nerve activity and increase active vasodilatation of the skin circulation in order to increase heat loss. The characteristic skin blood flow response in this setting exhibits a hockey stick shape, with a body core temperature (T_c) threshold for vasodilatation and a subsequent linear increase in blood flow as T_c continues to rise (Johnson & Proppe, 1996) (figure 1). If thermal stress becomes severe, skin blood flow can increase to maximal levels and reach an estimated 7.8 l/min over the entire body surface (Rowell, 1974).

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Given that heat is the most abundant byproduct of cellular metabolism, dynamic exercise in which a significant percentage of muscle mass is engaged (~ 50%) generates a thermal load that initiates cutaneous vascular responses similar to those described above. The skin blood flow response to acute dynamic exercise is modified from the response to passive thermal stress in a number of ways. Most notable are a rightward shift in the T_c threshold for vasodilatation and the presence of a plateau that occurs at a T_c of ~ 38°C, beyond which skin blood flow remains at 50–60% of maximal (Kenney & Johnson, 1992) (figure 1). These effects of exercise on the control of skin blood flow by T_c appear to result from the regulation of higher body temperature during exercise and the competing demands of the skeletal muscle and cutaneous circulations for cardiac output (Kenney & Johnson, 1992; Gonzalez-Alonso *et al.*, 2008).

One of the salient adaptations to endurance exercise training is an elevation in skin blood flow relative to core body temperature during exercise (Roberts *et al.*, 1977). This adaptation is achieved in part by earlier initiation of the active vasodilator system during exercise (Thomas *et al.*, 1999). In addition, contemporary studies suggest that the cutaneous vasculature exhibits functional adaptations to exercise training, including increased endothelium-dependent vasodilatation (Kvernmo *et al.*, 1998; Vassalle *et al.*, 2003; Franzoni *et al.*, 2004a; Lenasi & Strucl, 2004; Wang, 2005; Black *et al.*, 2008). These adaptations are reminiscent of those observed in the skeletal muscle circulation following exercise training (Jasperse & Laughlin, 2006). What are not clear are the signals associated with exercise that initiate these cutaneous vascular adaptations, and whether these adaptations play a functional role in the maintenance of higher skin blood flow (and reduced thermoregulatory strain) during exercise in the trained state.

The purpose of this Hot Topic review is to discuss the cutaneous vascular adaptations to exercise training in the context of training-mediated changes in thermoregulatory control during exercise. We conclude by posing the following question: what (if any) is the functional role of increased cutaneous microvascular reactivity following exercise training?

Control of skin blood flow during acute whole body dynamic exercise

The cutaneous vascular response to acute dynamic exercise involves a transient reduction in skin blood flow at the onset of exercise mediated by increased cutaneous sympathetic vasoconstrictor outflow (Blair *et al.*, 1961; Bevegard & Shepherd, 1966; Zelis *et al.*, 1969; Kellogg *et al.*, 1991). As dynamic exercise progresses, core temperature begins to rise while skin blood flow remains unchanged until a T_c threshold is reached beyond which skin blood flow begins to rise. This T_c threshold for vasodilatation is unaffected by peripheral blockade of adrenergic vasoconstrictor activity, suggesting it reflects the onset of active vasodilator activity during dynamic exercise.

As T_c rises beyond the threshold for cutaneous vasodilatation during sustained exercise, skin blood flow increases linearly with increasing core temperature until a point is reached (at a T_c of ~38°C) beyond which further increases in T_c elicit little or no further change in skin blood flow (Roberts *et al.*, 1977; Gonzalez-Alonso *et al.*, 1999) (figure 1). Beyond this "plateau", T_c continues to rise while skin blood flow remains at approximately 50–60% of maximal (Brengelmann *et al.*, 1977; Kellogg *et al.*, 1993; Johnson & Proppe, 1996). Several lines of evidence suggest this plateau in skin blood flow represents a limit imposed on the magnitude of skin blood flow by cardiopulmonary baroreflexes. First, no plateau in skin blood flow is observed during thermal stress to core temperatures well beyond 38°C in resting conditions (Johnson & Proppe, 1996). This suggests that dynamic exercise, and possibly the demand for cardiac output to active muscle and skin, imposes a limit on how high skin blood flow can increase when T_c is challenged. Second, the presence or absence of

this plateau is sensitive to acute manipulations of central blood volume by hypohydration (Nadel *et al.*, 1980), water immersion (Nielsen *et al.*, 1984), or saline infusion (Nose *et al.*, 1990), suggesting that cardiac filling pressure may be an important signal in the reflex that regulates this plateau in skin blood flow. Third, superimposing continuous negative pressure breathing during sustained exercise, which increases atrial transmural pressure and simulates increased cardiac filling, effectively eliminates the plateau in skin blood flow (Nagashima *et al.*, 1998). Taken together, these studies suggest that, during high intensity dynamic exercise, regional vascular conductance in the skeletal muscle and cutaneous circulations increase to the extent that arterial blood pressure regulation is challenged and cannot be regulated by cardiac output owing to a fall in cardiac filling pressure (Rowell, 1974). In this circumstance, it appears that blood flow to the skin is sacrificed at the expense of oxygen delivery to active skeletal muscle (Gonzalez-Alonso *et al.*, 2008).

Impact of endurance exercise training on the control of skin blood flow

Endurance exercise training results in modifications to the cutaneous vascular response during dynamic exercise described above. In the endurance trained state, the T_c threshold for vasodilatation is shifted leftward so that skin blood flow begins to rise at a lower T_c (Roberts *et al.*, 1977). Thomas et al. (1999) determined this leftward shift in the T_c threshold for vasodilatation is not influenced by changes in cutaneous sympathetic vasoconstriction; this suggests active vasodilatation is initiated at a lower T_c after training. Additionally, the magnitude of skin blood flow achieved in the plateau phase is increased after training (Fritzsche & Coyle, 2000; Takeno *et al.*, 2001). In contrast, most (Roberts *et al.*, 1977; Thomas *et al.*, 1999; Takeno *et al.*, 2001; Ichinose *et al.*, 2009) but not all (Hayashi *et al.*, 2009) studies indicate the slope of the relation between T_c and skin blood flow across the linear portion of this relationship is not sensitive to training status. Thus, training-induced modifications in cutaneous vascular control collectively result in higher skin blood flow (and presumably higher active vasodilator activity) for a given T_c during exercise (figure 1).

Endurance exercise training results in characteristic haemodynamic adaptations, including increased cardiac output and blood volume, which ultimately reduce circulatory strain and improve thermoregulatory capacity during exercise (Ekblom *et al.*, 1968; Convertino, 1991). It is thought that these adaptations, which are likely mediated to some extent by chronic exposure to increased T_c, result in an increased availability of blood volume for circulation through the cutaneous vasculature during exercise. Indeed, the expansion of blood and plasma volume after 10 days of heat acclimation also causes a leftward shift in the core temperature – skin blood flow relation (Roberts *et al.*, 1977), suggesting that haemodynamic adaptations alone may be sufficient to modify the control of skin blood flow during exercise. Recently, this hypothesis was directly tested by elimination of the plasma volume expansion associated with exercise training in the heat. Ikegawa et al (2011) trained seven men in the heat for 5 days (30 min/day @ 70% VO_2max) and performed both euhydrated and hypohydrated thermoregulatory exercise tests before and after training (measuring forearm skin blood flow, T_c, etc). After training in the heat, plasma volume increased (11%) when comparing euhydrated conditions, while plasma volume was not different pre- vs. post-training in hypohydrated conditions. Comparison of the effect of heat training on euhydrated and hypohydrated thermoregulatory exercise test performance demonstrated that *removal of the plasma volume expansion associated with training eliminated both the leftward shift in T_c threshold and the difference in peak skin blood flow during exercise*. These results strongly suggest training-induced adaptations in the control of skin blood flow during exercise are critically dependent on expansion of blood/plasma volume and the resultant changes in central blood volume during exercise.

Local cutaneous vascular adaptations to endurance exercise training

The similarity of the slope across the linear portion of the T_c – skin blood flow relationship (before and after training) suggests peripheral adaptations are not responsible for training-induced changes in the control of skin blood flow. That is, the cutaneous vasculature does not appear to adapt with respect to the sensitivity of the active vasodilator response. In contrast, exercise training is associated with increased cutaneous vascular responsiveness to several modes of local stimulation; these adaptations are reminiscent of those observed in the skeletal muscle vasculature following endurance exercise training (for review of skeletal muscle vascular adaptations see Jasperse and Laughlin (2006)). Below we review the evidence for a training effect on three different assays of cutaneous microvascular reactivity and the potential mechanisms responsible for these vascular adaptations.

Young subjects

Acetylcholine Iontophoresis—Most (Kvernmo *et al.*, 1998; Lenasi & Strucl, 2004; Wang, 2005) but not all (Boegli *et al.*, 2003) studies of young healthy subjects suggest responsiveness of the cutaneous circulation to the iontophoresis of Acetylcholine (Ach) is increased in the exercise trained state. For example, Kvernmo et al. (1998) tested cutaneous vascular responses to iontophoresis of Ach and sodium nitroprusside (SNP) in elite endurance athletes (VO_2 max = 69.8 ml/kg/min) and young, recreationally active volunteers and found the skin of the endurance athletes to be more responsive to Ach at the lowest dose administered. In contrast, endothelium-independent responses to SNP were not different between groups. Using a longitudinal design, Wang (2005) exercise trained 10 sedentary but otherwise healthy males for 8 weeks (30 minutes/day @ 50% VO_2 max, 5 days/week), and tested cutaneous vascular responses to Ach and SNP pre and post training. After completing the exercise training period, cutaneous vascular responsiveness to Ach was increased while responses to SNP were unchanged. These findings suggest endothelium-dependent cutaneous vasodilatation is improved by exercise training. Unfortunately, the endothelium-dependent pathways through which Ach induces vasodilatation in the skin are complex and only partially understood (Morris & Shore, 1996; Kellogg *et al.*, 2003; Boutsiouki *et al.*, 2004; Durand *et al.*, 2004; Holowatz *et al.*, 2005); it remains unclear which of these pathways are affected by exercise training (e.g., prostanoids, nitric oxide, etc).

Local Heating—The cutaneous vascular response to local skin heating is comprised of an initial axon-reflex mediated peak in blood flow followed by a secondary rise to a sustained plateau after roughly 20–30 minutes (Minson, 2010). The secondary plateau phase of the local heating response is largely nitric oxide-mediated (Kellogg *et al.*, 1999; Minson *et al.*, 2001). Skin blood flow during the nitric oxide-dependent plateau phase is higher in endurance trained adolescents compared to matched sedentary controls (Roche *et al.*, 2010). In contrast, the initial peak in skin blood flow appears to be uninfluenced by training status in young healthy subjects (Tew *et al.*, 2011). These results suggest that endurance exercise training promotes increased nitric oxide bioavailability in the cutaneous microvasculature; this mechanism could be responsible for increased Ach-mediated cutaneous vasodilatation as well.

Reactive Hyperaemia—Using cutaneous reactive hyperaemia, Lenasi and Strucl (2004) and Vassalle et al. (2003) compared cutaneous vascular reactivity between endurance trained athletes and age and BMI matched sedentary controls. These studies evaluated different metrics of the blood flow response following a period of total limb occlusion (3 – 8 min); one study assessed the area und the curve (Lenasi & Strucl, 2004) while the other assessed only the peak of the blood flow response (Vassalle *et al.*, 2003). Both studies demonstrated greater reactive hyperemia in the trained subjects. In addition, Franzoni et al.

(2004b) demonstrated the magnitude of reactive hyperaemia was directly correlated to total plasma antioxidant capacity, suggesting that greater antioxidant defenses may be a feature of cutaneous vascular adaptation to exercise training. Inasmuch as reactive hyperaemia in the cutaneous circulation is not dependent on nitric oxide (Wong *et al.*, 2003; Zhao *et al.*, 2004) nor cyclooxygenase-derived prostanoids (Lorenzo & Minson, 2007), these combined results suggest that other vasomotor pathways contributing to reactive hyperaemia in the skin may be affected by exercise training (e.g., sensory nerves and BKCa channels (Lorenzo & Minson, 2007)).

Aging

Human aging in the absence of overt pathology is associated with an attenuated reflex vasodilator response during exercise heat stress (Anderson & Kenney, 1987; Kenney, 1988; Ho *et al.*, 1997). This impaired skin blood flow response is apparent even when subjects are matched for fitness level (Ho *et al.*, 1997), acclimation status (Armstrong & Kenney, 1993), and hydration status (Kenney *et al.*, 1990). Peripheral vascular impairments in aged skin include both up- and downstream neurovascular signaling mechanisms mediating reflex vasodilation, including an increased reliance on attenuated NO-dependent vasodilation (Holowatz *et al.*, 2003).

A number of studies have investigated the effects of exercise training (or training status) on cutaneous microvascular reactivity in healthy aging populations. These studies have shown that Ach-mediated vascular responses in the skin are increased by exercise training (Black *et al.*, 2008; Hodges *et al.*, 2010), although this is not a universal finding (Tew *et al.*, 2010). In one well controlled study, Black et al. (2008) blocked nitric oxide production with cutaneous microdialysis of L-NAME (NO synthase inhibitor) during Ach infusions and demonstrated that increased vascular responsiveness following 24 weeks of exercise training was achieved through the increased actions of nitric oxide in the skin. To our knowledge, this study represents the only use of microdialysis and selective pathway inhibitors to investigate the mechanisms of increased cutaneous vasomotor responses following endurance exercise training in any population.

In addition to Ach responses, both the local thermal hyperaemia and reactive hyperemic responses appear to be augmented by exercise training in the aged (Franzoni *et al.*, 2004a; Black *et al.*, 2008; Hodges *et al.*, 2010; Tew *et al.*, 2010). Interestingly, both the initial peak (Tew *et al.*, 2010; Tew *et al.*, 2011) and sustained plateau (Black *et al.*, 2008; Hodges *et al.*, 2010; Tew *et al.*, 2010) portion of the thermal hyperemic response are augmented in trained older subjects. The increased initial peak response during local heating in trained older subjects is normalized following administration of local anesthetic, suggesting sensory nerve-mediated vasomotor responses as well as nitric oxide production are increased by training in this population (Tew *et al.*, 2011).

Proposed signals mediating cutaneous vascular adaptations to endurance exercise training

The signaling events responsible for the cutaneous vascular adaptations to endurance exercise training are unknown. Endurance exercise training typically involves the completion of frequent bouts of whole body dynamic exercise lasting 30 – 60 minutes per session (40 – 80% VO_2 max; 3 – 7 days/week). Exercise sessions of this type cause an elevation in T_c that stimulates increases in thermoregulatory skin blood flow, as described above. As a result, the cutaneous circulation is exposed to chronic elevations in perfusion during training, suggesting that haemodynamic forces may provide a key signal for training-induced adaptations in the cutaneous circulation. It is well established that haemodynamic forces associated with increased blood flow during exercise (e.g., shear stress, cyclic strain,

etc) are primary signals for the vascular adaptations that occur in the previously trained skeletal muscle (Laughlin *et al.*, 2008). Notwithstanding significant anatomical differences that exist between skeletal muscle and cutaneous vascular beds, some recent findings support the hypothesis that haemodynamic forces are responsible for the transduction of exercise training-mediated adaptations in the cutaneous vasculature. A recent study by Green *et al.* (2010) examined the hypothesis that repeated forearm heating, which increases skin blood flow in the absence of exercise, improves cutaneous microvascular vasodilator function. In this study, bilateral forearm heating to 42°C (via water immersion) was applied to ten healthy men for 30 min, 3 times per week for 8 weeks. During the immersion sessions, skin blood flow was manipulated in one arm by inflation of a proximal forearm cuff to 100 mmHg, while the other arm remained uncuffed. This manipulation allowed determination of the role of chronic increases in perfusion *per se* in the cutaneous vascular adaptations to repeated skin heating. After 8 weeks of repeated limb heating, the cutaneous vascular response to acute local heating (thermal hyperaemia) was increased in the uncuffed arm (i.e., the arm with the greatest chronic increase in perfusion) whereas it remained unchanged in the cuffed arm (Green *et al.*, 2010). Because changes in tissue perfusion are often related to changes in vascular wall shear stress, these results support the hypothesis that haemodynamic forces are responsible for the transduction of exercise training-induced vascular adaptations in the skin circulation.

Functional relevance of local cutaneous vascular adaptations to exercise training?

A persistent question in this area is the degree to which exercise training-mediated increases in cutaneous vascular responsiveness bear any functional relevance to the control of skin blood flow during dynamic exercise. That is, training-induced modifications to the control of skin blood flow during exercise appear to be explained by expansions to plasma volume and a subsequent increase in the available cardiac output to meet the competing needs of increasing skeletal muscle and cutaneous vascular conductances (see above). Therefore, although adaptations in cutaneous microvascular reactivity have been demonstrated using a variety of techniques, it does not appear that these adaptations are critical to either the shift in T_c threshold for vasodilatation or the increased skin blood flow during the plateau phase following exercise training. Furthermore, most of the cutaneous vascular adaptations observed in the exercise trained state are suggestive of adaptations in the microvascular endothelium (Kvernmo *et al.*, 1998; Vassalle *et al.*, 2003; Franzoni *et al.*, 2004a; Lenasi & Strucl, 2004; Wang, 2005; Black *et al.*, 2008). Considering the litany of compounds implicated in the active vasodilator response (e.g., vasoactive intestinal polypeptide, histamine, etc), it is not clear that these substances arise from or act through endothelial cells to effect thermoregulatory vasodilatation during exercise (Kellogg *et al.*, 1995; Kellogg *et al.*, 2003; Wong *et al.*, 2004; Wilkins *et al.*, 2005; McCord *et al.*, 2006; Wong & Minson, 2006). Even nitric oxide, responsible for 30–45% of the active vasodilator response, may be generated by the neuronal isoform of nitric oxide synthase (Kellogg *et al.*, 2009). Thus, a synthesis of available literature does not support the hypothesis that local cutaneous vascular adaptations are responsible for training-mediated changes in the control of skin blood flow during exercise, at least in young healthy individuals.

In the context of primary aging, it is possible that training-induced cutaneous vascular adaptations are more critical for changes in the control of skin blood flow during exercise. As mentioned above, primary aging is associated with a reduced ability to increase skin blood flow during exercise thermal stress, due in part to reductions in cardiac output (Kenney, 1988), reductions in the redistribution of blood flow from renal and splanchnic beds (Ho *et al.*, 1997), and decrements in cutaneous microvascular function (Holowatz & Kenney, 2010). Thus, it is possible that exercise training-mediated cutaneous vascular

adaptations are required to permit the increased skin blood flow during exercise observed following training in this population (Ho *et al.*, 1997). In support of this concept, some studies indicate the slope of the relation between T_c and skin blood flow is reduced in aged compared to younger populations (Kenney, 1988), while additional (limited) evidence suggests this slope is increased when aging subjects undergo endurance training (Ho *et al.*, 1997). This raises the possibility that, in aging, the cutaneous vasculature can adapt with respect to its sensitivity to active vasodilator activity following training.

Conclusions

In summary, endurance exercise training causes adaptations in the skin blood flow response to exercise, inclusive of changes in cutaneous microvascular reactivity. Increases in skin blood flow at a given exercise core temperature appear to be primarily explained by the expansion of blood volume and increased cardiac output that characterize the trained state. In contrast, adaptations in the cutaneous microvasculature are mediated by changes in the bioavailability or bioactivity of endothelium-derived vasoactive compounds; however, the mechanistic basis for these adaptations remains largely unexplored. Present evidence does not support a causal relation between these two training-mediated adaptations in young healthy persons. That is, it does not appear that skin blood flow during exercise is higher after training *because of* local cutaneous microvascular adaptations. However, training-mediated vascular adaptations in the skin may be important against a background of preexisting microvascular dysfunction (e.g., in aging).

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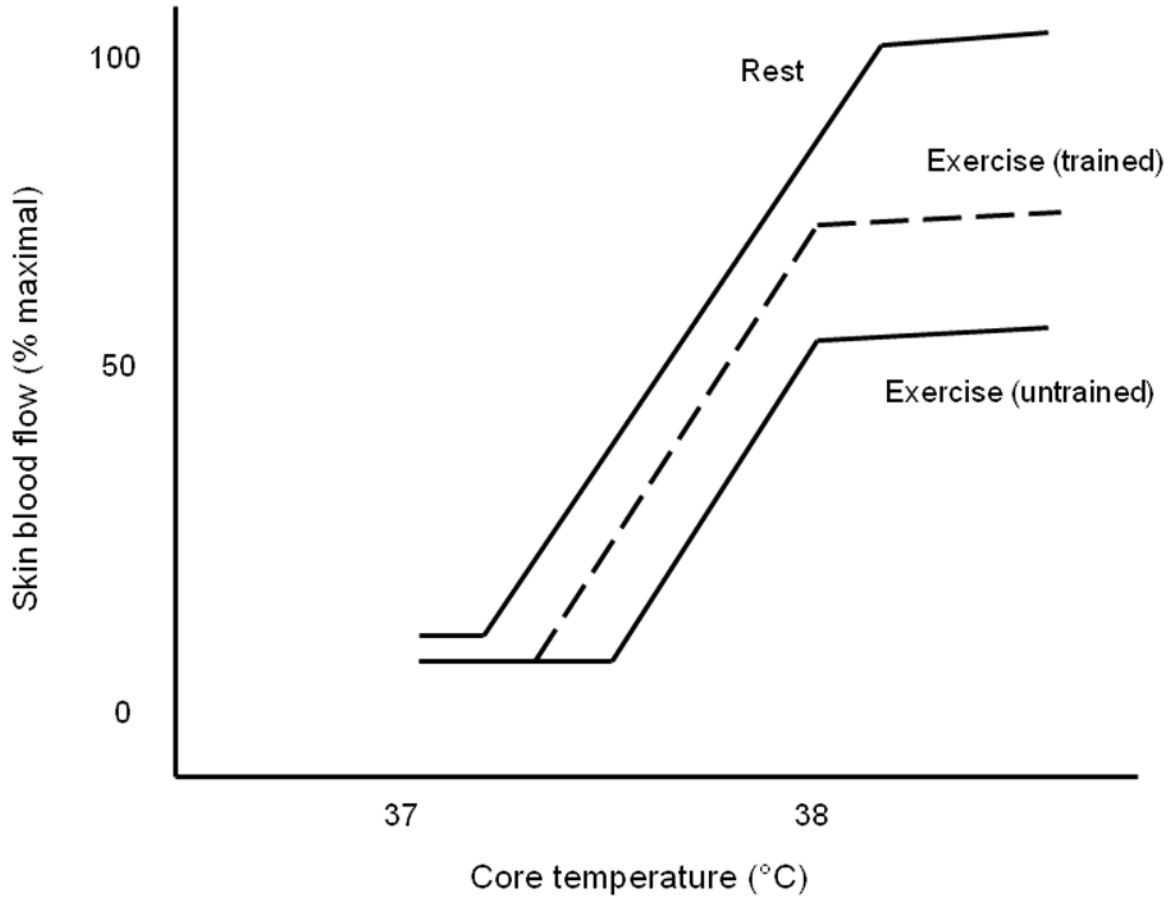

Figure 1.
Schematic representing the relation between skin blood flow and core body temperature during thermal stress at rest, during acute exercise in the untrained state, and during acute exercise in the endurance exercise trained condition.