PERIODICUM BIOLOGORUM
VOL. 116, No 1, 21–28, 2014

UDC 57:61
CODEN PDBIAD
ISSN 0031-5362

Physical exercise and skin microcirculation

HELENA LENASI

University of Ljubljana, Medical Faculty,
Institute of Physiology,
Zaloška 4, 1000 Ljubljana, Slovenia,
E-mail: helena.lenasi.ml@mf.uni-lj.si

Key words: skin microcirculation, exercise, laser Doppler flowmetry, vasodilation, thermal homeostasis

Abbreviations:
SkBF, skin blood flow
CVC, cutaneous vascular conductance
AVAs, arteriovenous anastomoses
LDF, laser Doppler flowmetry
CVS, cardiovascular system
V_{02max}, maximal aerobic capacity
HR, heart rate
MAP, mean arterial pressure

Received February 21, 2014.

Abstract

One of the main role of skin is its involvement in thermoregulation. Skin blood flow (SkBF) is subject to great variations, depending on the environmental and body thermal status. Physical exercise imposes heat stress for the body and thus skin microcirculation. To achieve thermal homeostasis, SkBF and sweating are increased in response to exercise. The thermoregulatory response of SkBF during exercise differs from that at rest in the threshold for vasodilation and the sensitivity of the "SkBF-to-core temperature slope". The purpose of this review is to highlight the response of skin microcirculation to physical exercise.

INTRODUCTION

Dynamic exercise strongly affects skin microcirculation as skin is the main effector organ for heat elimination. During dynamic exercise, the production of heat in the working skeletal muscles increases tremendously inducing an increase in core temperature. Additional heat needs to be eliminated in order to achieve thermal homeostasis; thermoregulatory reflexes induce adjustments of cutaneous vascular conductance (CVC) and thus SkBF and sweating rate. The amount of changes depends on the intensity, type and duration of exercise as well as on environmental temperature. It has been estimated that skin blood flow during extreme exercise in a hot environment can attain up to 7 L/min as compared to 300 ml/min at rest in thermoneutral conditions *(1, 2)*. Apart from thermal reflexes, different nonthermal reflexes that tend to diminish SkBF in order to obtain enough oxygen and nutrients to the working skeletal muscles and the heart are activated during exercise *(3)*. How these conflicting reflexes integrate at the level of skin microcirculation and how they impact thermoregulation is the focus of this review.

Functional organization of skin microcirculation

One of the main features of skin microcirculation is its large surface that makes skin a suitable organ for the exchange of heat between the body and the environment. Most blood vessels are situated in the dermis where they form a papillary plexus, made up of high-resistance arterioles, papillary loops and postcapillary venules. The papillary loops are located close to the dermal-epidermal junction what enables a great temperature gradient between the blood and epidermal tissues *(4, 5)*. It is at the level of arterioles where the fine tuning of vascular tone is accomplished.

Worth to note is the different anatomical organization of skin microcirculation in different parts of the body. Most of the body is covered

with hairy or so called non-glabrous skin whereas acral, nonhairy or glabrous skin covers acral parts of the body, such as lips, ears, nose, palms, soles and finger and toe pulps. Special features of acral skin are direct connections between arterioles and venules called arteriovenous anastomoses (AVAs) that when opened enable large increases of blood flow through these very areas. SkBF in glabrous skin exhibits large spontaneous fluctuations, most probably reflecting changes of blood flow through AVAs, which are synchronous over the body *(6)*. These oscillations are most pronounced in thermoneutral conditions and are thought to contribute to maintaining a stable core temperature. In resting thermoneutral conditions they constrict 3-4 times a minute and have been shown to correlate with blood pressure and heart rate variability. The fluctuations are abolished when AVAs remain mainly closed or mainly opened *(7)*.

The division of skin into these two parts seems logical also from the mechanistic point of view as the control of blood flow in these two parts differs.

Regulation of skin blood flow in resting thermoneutral conditions

From the above estimations of wide variations of skin blood flow in response to thermal challenges it is obvious that the regulation of SkBF is complex. In spite of many investigations trying to elucidate the exact mechanisms of SkBF regulation many questions remain unresolved.

The main mechanism of arteriolar tone regulation is neural mechanism. Acral, glabrous parts of the skin are solely under the influence of the sympathetic noradrenergic vasoconstrictor system that releases noradrenalin, acting on postsynaptic α_1- and α_2-adrenergic receptors, along with potential cotransmitters (such as neuropeptide Y). On the other hand, the non-glabrous nonacral parts apart from the sympathetic noradrenergic vasoconstrictor fibers also receive a separate sympathetic cholinergic active vasodilatory nerve fibers *(8, 9, 10)*. The existence of two separate systems has been confirmed in many independent studies by the observation that local application of bretylium to block the presynaptic release of noradrenalin from the sympathetic nerve fibers abolished the cutaneous vasoconstriction induced by cold stress whereas the vasodilator responses induced by heat were not affected. The vasodilator system has been most frequently investigated in the last years, yet the exact transmitter has not unequivocally been confirmed. Cholinergic fibers as well as cotransmission from sudomotor fibers have been suggested to be involved in active vasodilation with a range of proposed mediators: bradykinin, nitric oxide (NO), prostaglandins, vasoactive intestinal peptide (VIP), calcitonin gene- related peptide (CGRP), substance P, histamine *(3, 8, 9, 10, 11)*. It has been proposed that 30-40% of active vasodilation could be attributed to NO from neuronal NO synthase pointing to a presynaptic release of NO *(12)*.

Both, the vasoconstrictor and the vasodilator system are subject to modulations by different afferents, such as skin afferents *(10, 13, 14)*, afferents from mechano- and metaboreceptors from the working skeletal muscles *(15, 16, 17, 18)*, as well as baroreflex *(11, 19, 20)* and modifiers from central origin (so called central command). Furthermore, SkBF is affected by time of the day *(21)*, gender and the female menstrual cycle *(11, 22, 23),* endurance status *(24, 25)*, as well as age *(26)* and disease *(9)*.

Other modulators of vascular tone include local factors. The most important local regulator of vascular tone is local temperature: local heating and cooling of skin induces subtle changes in the basal vascular tone that finally impact the regulation of skin blood flow *(8, 13, 27)*. Furthermore, the role of endothelium should not be underestimated. For example, NO released form endothelium has been shown to modulate the presynaptic release of noradrenalin by modifying presynaptic α_2-receptors *(28, 29)*. In spite of conflicting results from different studies, endothelial vasodilators, such as prostaglandins, NO and endothelium-derived hyperpolarizing factor (EDHF) most probably all contribute to local adjustments of the vascular tone *(30, 31, 32)*; the exact contribution of each probably depends on age and (dys)functional endothelium and has to be elucidated in further studies.

At rest and thermoneutral condition the cutaneous vessels are under the tonic influence of vasoconstrictor fibers whereas the vasodilator system is not active *(3, 10)*; in this setting skin blood flow is estimated to be approximately 300 mL/min and as such comprises 5% of the cardiac output and results in a heat dissipation of 80 to 90 kcal/h *(3, 11)*. How tremendously it can change in response to heat stress will be elucidated below.

Methodological considerations: how to study and challenge skin microcirculation

The cutaneous microcirculation represents an easily accessible and potentially representative vascular bed to examine the mechanisms of microcirculatory function and dysfunction. Mostly used method is laser Doppler flowmetry (LDF) that enables a semiquantitative assessment of SkBF *(6, 33, 34, 35)*. Its great advantage is noninvasiveness and easy applicability. Further, it measures blood flow in superficial tissues such as skin and enables a good estimation of SkBF as opposed to plethysmography that besides from skin also measures blood flow in the underlying muscles. Its pitfalls are great spatial and temporal variability. Besides from LDF newer promising methods appeared, such as laser Doppler imaging, magnetic resonance imaging, electron paramagnetic resonance, sidestream dark field imaging *(34, 36, 37)*.

The best way to determine the relationship of SkBf to core and skin temperature is to simultaneously trace skin temperature at the corresponding sites measured by LDF

along with core temperature. Core temperature has usually been obtained by esophageal probe or by tracing of the tympanic temperature by an ear probe *(38)*.

Passive thermal challenge could either be performed by thermally insulated suits to stimulate changes of core temperature or by local thermal provocations to change skin temperature *(8, 13, 27)*. Exercise challenge could either be dynamic exercise that encompasses large muscle mass or static isometric exercise.

The response of SkBF to thermoregulatory challenge during exercise differs from that at rest

During a thermal challenge, skin blood flow responds to changes in the internal (core) temperature sensed by central thermoreceptors as well as skin temperature sensed by peripheral (skin) thermoreceptors that are the major sensory component. The primary mechanism for stimulating heat loss is the hypothalamic feed-back circuit which receives an integrated signal from core and skin temperature *(11, 39)*. In conditions of maximal heat stress, about 60 % of cardiac output can be shifted to the skin; in this setting, SkBF can reach up to 7 L/min *(1, 2)*, what imposes a significant cardiovascular challenge.

It has been estimated that during significant body heat stress, about 80-90% of the increase in SkBF could be attributed to increased activity of the vasodilator system, whereas only 10% is a consequence of the withdrawal of the sympathetic vasoconstrictor system activity *(3, 10, 11)*.

During whole body passive heating (in resting conditions), first of all, the vasoconstrictor system activity is withdrawn in both, glabrous and non-glabrous skin resulting in increased CVC. It is not until the internal temperature has reached the threshold that the cutaneous vasodilator system in non-glabrous skin is activated, leading to significant increase of CVC in these areas. The sensitivity of the cutaneous circulation to elevation in core temperature is usually represented by the slope of SkBF to core temperature relationship.

Dynamic exercise is known to affect skin blood flow through several modifications of the vasoconstrictor and active vasodilator system *(3, 8, 40)*. The main difference in thermal adaptation between rest and exercise is that during dynamic exercise the cardiovascular system (CVS) is challenged by thermal as well as other opposing reflexes that tend to maintain blood pressure and favor redistribution of blood flow to metabolically active tissues to increase the supply of oxygen and nutrients. The CVS accomplishes the task by an increase in cardiac output and by redistribution of blood flow *(1, 2)* that finally result in an altered response of skin microcirculation to a thermal challenge. Based on the external stimuli, the haemodynamic responses to environmental stress and exercise are determined by the magnitude of the environmental (heat or cold) load and the duration, intensity and type of exercise *(41)*.

The main differences of the response of SkBF to a heat challenge between rest and exercise are listed below.

First of all, the initial, baseline tone of skin vessels is increased in exercise as a consequence of redistribution of blood flow to the exercising muscles at the beginning of exercise *(1, 2, 3, 10)*. Furthermore, it has been shown in many independent studies that the threshold temperature to induce vasodilation is shifted to higher internal temperature during exercise as compared to rest *(1, 2, 3, 9, 10)*. The mechanisms of increased threshold have not been elucidated. With increasing exercise intensity, the threshold is displaced to even higher temperatures, thus compromising heat elimination *(3, 9, 14, 42, 43)*. This seems logical as with increasing intensity the demand of working skeletal muscle and the heart for oxygen is increased. This mismatch could in the worst scenario lead to hyperthermia what is usually not the case, especially in thermoneutral environment, as increased core temperature compromises the functioning of skeletal muscles and results in fatigue *(2)*. Moreover, during exercise, the maximal vasodilation of skin reaches a plateau that is only 60 % of the maximal vasodilation due to a heat challenge, seen at rest *(2, 3, 10)*. It is suggested that this is mainly a reflection of modifications of the vasodilator system rather than superimposing increased vasoconstrictor activity; the exact mechanism has not been revealed yet. Pooling of blood in the skin vessels that in turn compromises cardiac filling and activates baroreflex have been proposed as well as changes in osmolarity and plasma volume *(2)*. Although it has been claimed that exercise limits the vasodilator outflow centrally, inhibition of active cutaneous vasodilation by muscle metabo- and mechanoreceptors has also been suggested *(15, 18)*.

Mechanistically, the response of SkBf flow to exercise could be divided in an initial response, in the response to sustained exercise and in the response to recovery from exercise.

At the beginning of exercise there is a decrease of CVC throughout the body that undoubtedly reflects the increased sympathetic vasoconstrictor activity brought about by the central command *(2, 3)*. The extent of this initial vasoconstriction is, in turn, dependent on the intensity of exercise, more to absolute intensity than to relative load *(2)*. Later during exercise, it is more the relative load, expressed as % of maximal aerobic capacity (V_{O2max}) that preferentially determines the changes of skin blood flow, according to the extent of metabolically produced heat. Logically, the degree of initial vasoconstriction also depends on the active muscle mass and the mode of exercise (static vs. dynamic). The initial vasoconstrictor response is limited to the adrenergic vasoconstrictor nerves *(2, 10)*. It has been shown that blockade of

vasoconstrictor function with iontophoretically applied bretylium abolished the response in normothermic conditions and also during elevated body temperature when the active vasodilator system was engaged *(44)*.

As exercise continues the internal temperature reaches the threshold that activates the vasodilatory fibers in non-glabrous skin. An interesting observation is that the threshold for increased sweating during exercise is not affected by the intensity of exercise *(2)*. Namely, this is not the case for most other nonthermoregulatory reflexes, which mostly affect vasodilator and sudomotor threshold in the same way. Most studies focused on non-glabrous skin, whereas the response of glabrous skin has not been investigated.

Last but not least, we would like to imply the importance of endothelium in the regulation of CVC during exercise: in the settings of increased blood flow the shear stress is increased leading to increased production of endothelial vasodilators that subsequently lead to vasodilation and in this respect augment the CVC increment. Indeed, it has been shown in the studies which performed spectral analysis of SkBF oscillations that the amplitude of the low frequency oscillations presumably reflecting endothelial function is changed in response to exercise as compared to rest *(45, 46)*. This implies the role of endothelium in the regulation of blood flow during exercise.

After the cessation of exercise sympathetic tone is withdrawn reflected by a decrease of heart rate (HR) and an abrupt fall of mean arterial pressure (MAP). The fall of MAP is offset by the activation of baroreflex *(3, 19, 20, 47, 48)*. Yet, it has been postulated that baroreflex is reset after exercise, partly explaining the prolonged hypotension that is known to persist far beyond the cessation of exercise *(20, 47, 48, 49)*. Moreover, the increased CVC above the resting conditions could partly explain the hypotension in the recovery. Vasodilator system in skin microcirculation remains activated as long as the core temperature remains elevated above the threshold. Studies have shown that the contribution of the above mentioned reflexes to the regulation of SkBF in the recovery period is strongly dependent on the mode of recovery: during inactive recovery, baroreceptors are suggested to be primarily involved while muscle pump and central command activated during active recovery diminish the baroreflex *(48, 50)*.

Many factors can alter either the threshold or/and the sensitivity of the slope, such as skin temperature *(2, 3, 14)*, blood volume and osmolarity *(2, 40, 51)*, and posture *(19, 52)* acutely, and, on a longer term basis, heat acclimation *(53)*, exercise training *(24, 25, 54)*, circadian rhythm *(21)*, and reproductive hormone status in women *(11, 23)*. While acute adjustments of SkBF to thermoregulatory and nonthermoregulatory challenges are achieved mainly through modifications of vasodilator and to a lesser extent of vasoconstrictor nerves, chronic changes, such as in response to acclimation or endurance training are most probably brought about by structural and endocrine changes *(2, 38)*.

An interesting issue is the impact of skin temperature, reflecting environmental and body conditions, on the regulation of SkBF. Peripheral skin thermoreceptors sense alterations of ambient temperature and modulate the response of central reflexes: the threshold for vasodilation has been shown to be shifted to lower core temperature at higher ambiental and skin temperatures *(2, 14, 40, 55, 56)* and vice versa, i.e. to higher internal temperatures at low ambiental temperatures what enables a better preservation of heat in a cool environment *(2, 57)*. Low skin temperature has been suggested to affect mainly the vasodilatory fibers and not the vasoconstrictory ones *(2)*. An interesting observation regarding the effect of skin temperature on thermoregulation was presented by Demachi *et al.* who found a difference in the modification by skin temperature of the central control of cutaneous vasomotor tone at different levels of exercise *(14)*.

Aerobic capacity and performance have been shown to be strongly affected by skin temperature: V_{O2max} was significantly reduced with increased skin temperature independent of core temperature *(56)*. This seems logical as increased skin temperature during exercise reduces the temperature gradient for heat elimination and thus impedes the heat exchange. To surpass the decreased temperature gradient, SkBF is increased on account of diminished blood flow through skeletal muscles. Furthermore, pooling of additional blood in the periphery impedes venous return, and activates baroreflex, leading to 'cardiovascular drift' *(1, 57, 58)*.

Prolonged whole-body exercise in the heat is associated with increased cardiovascular drift, i.e. greater tachycardia, skin and core hyperthermia and might compromise the cardiac output *(2, 11, 40, 57)*. It has been shown that the cardiac output was 1.5 L/min lower in a hot environment compared to thermoneutral conditions at the same exercise intensity in spite of a 20-beat increase of HR *(1, 57)*. Another problem in a hot environment is water and electrolite loss. The threshold for active vasodilation has been shown to depend on hydration status: it is shifted to higher core temperature in hypovolemia, additionally compromising heat loss and thus increasing the risk of hyperthermia *(3, 41, 59)*.

Sweating is the main effector mechanism for heat elimination during exercise

Alterations in CVC in response to a thermal challenge have inseparably been connected to sweating. The evaporation of sweat from the body surface represents one of the most important thermoregulatory mechanisms for eliminating excess heat from the body. In fact, evapora-

tion is the only mechanism for heat elimination in a hot environment where no temperature gradient exists between the surface of the body and the environment. A change of water state from the liquid to the gaseous phase consumes energy – heat that has been delivered to the skin surface and in this way cools the skin surface *(1, 57)*. Evaporative water heat is estimated to be 2,5 kJ/g water *(57)*. A decrease of skin temperature increases the temperature gradient between the body and the surface and thus augments the conductive heat loss. The sweat glands can deliver sweat to the skin surface at rates up to about 30 g/min and the maximum rate of sweat is estimated to comprise 2-4 L/h *(1, 57)*. It is thus obvious that apart from eliminating excess heat from the body, sweating is inevitably associated with fluid and electrolyte loss that need to be replaced. The efficiency of evaporation depends both, on physiological and environmental factors (such as humidity).

The control of sweating has been shown to be strongly connected to the control of CVC. Sweat glands are innervated by cholinergic sympathetic fibers that have been shown to be modulated by different substances: substance P, CGRP, VIP, atrial natriuretic peptide and NO; nevertheless, the exact interplay remains elusive *(3, 10, 55)*. Besides cholinergic fibers, sweat glands also possess α- and β- adrenergic fibers whose role in thermoregulation remains minor: they have been suggested to contribute only 10% to active thermoregulatory sweating during moderate exercise, while during intense exercise, the greatly increased plasma concentrations of adrenaline and noradrenaline to contribute to their activation *(55)*.

It has been shown in many independent studies that sweat rate increases at the very beginning of exercise before the core temperature has reached the threshold for active vasodilation pointing to the role of central command *(3, 55)*. Yet, while the rate of sweat secretion is almost immediate upon the start of exercise, there is a significant delay in the evaporation of the sweat accumulated on the skin surface what results in an increase of core temperature *(3)*. With prolongation of exercise, the increased core temperature additionally activates thermoregulatory reflexes leading to increased sweat production. Sweat rate increases linearly with an increase of exercise intensity *(3, 55)*. Increasing exercise intensity induces alterations of the sweat composition, sweat is more diluted *(1, 57, 60)*. Similar changes in the sweat rate and composition are observed upon acclimation to extreme environmental temperatures or in endurance trained sportsmen *(53, 61, 62)*. Contrary to CVC, exercise intensity does not alter the onset threshold for sweating even in a hypohydrated state *(3)*; yet, the threshold depends on the site *(3, 63)*. As for the effect of exercise intensity on the sensitivity of sudomotor response the results are inconclusive; differences might be attributed to huge regional differences in the distribution and activity of sweat glands *(42, 55, 63, 64)*.

The effect of gender on thermoregulation

Many studies focused on the effect of gender on human thermoregulation, with respect to the control of CVC and sweating during exercise; yet, there are many controversies *(3, 9, 22, 48, 62, 65)*. Due to cyclic changes of female reproductive hormones, SkBF in women is also subject to cyclic variations in resting conditions *(3, 9)*. It has been established that the threshold for the onset of cutaneous vasodilation and sweating is shifted to higher internal temperatures in the midluteal phase of the menstural cycle, probably reflecting combined central effects of increased levels of progesteron and estrogens in this very phase *(3, 10)*. Another interesting feature of luteal phase hormones is that they appear to increase the plateau level of SkBF during exercise in a warm environment *(3)*. This may offset the effect of the increased threshold for vasodilation seen during the luteal phase in terms of overall heat dissipation during prolonged exercise. Studies have shown that at the same exercise intensity (expressed in terms of % of V_{O2max}), the rate of sweating was lower in women as compared to men and the sensitivity of the sudomotor reflexes was lower in women *(22, 55, 65)*. The slope of the "sweating-to-core temperature" curve was less steep in women *(65)* in spite of the fact that the density of sweat glands is greater in women *(66)*. The mentioned differences have been shown to be more pronounced when women exercised at higher intensities of exercise (expressed in terms of % of V_{O2max}) *(22)*. Studies to determine potential changes in the threshold and the sensitivity for active vasodilation yielded contradictory results: while some failed to confirm significant differences between men and women in spite of different hormonal status *(22)*, there are reports which showed that the threshold for active vasodilation in the recovery to exercise was increased in women compared to men *(67)*. Apart from differences in hormonal status affecting peripheral mechanism, differences in central mechanism have been suggested *(48)*.

Last but not least, the potential differences between men and women regarding thermoregulation might also be accounted to physical sex characteristics, such as body surface to volume ratio and the subcutaneous fat differences.

Different regions of the skin respond differently to exercise

Although different studies aimed at elucidating the exact interplay of the mentioned mechanisms during and following exercise, only few studies simultaneously assessed the response in glabrous and non-glabrous skin. As these two areas differ in anatomical organization and innervation, it is tempting to speculate that they also respond differently to exercise. Apparently, the response of skin blood flow to acute exercise differs with regard to the

measuring site, and depends on exercise intensity, the mode of exercise and the position of the subject *(8, 10, 42, 52)*. It has bees established that there are regional differences in the threshold for vasodilation in response to an increase in exercise intensity *(3, 42)*. It has also been suggested that glabrous skin with AVAs is more prone to nonthermoregulatory demands than non-glabrous skin *(52)*. This seems logical as blood flow even under resting conditions is much higher in these areas.

Saad *et al*. showed that static isometric exercise elicits a reduction of CVC accompanied by a decrease of fluctuations of SkBF typical for the resting conditions in glabrous skin while the CVC on the volar forearm did not change during exercise *(68)*. On the other hand, Kondo *et al*. have shown that handgrip exercise of short duration induces sweating that is modulated by afferent signals from muscle metaboreceptors in the non-glabrous but not in the glabrous regions *(18)*. Yamazaki found increased amplitude of CVC in the palm compared to the forearm as well as an increased phase lag in the palm during sinusoidal exercise *(69, 70)*. The differences may partly be explained by different intensities of exercise used in different studies that might have shifted the threshold for vasodilation.

In our recent study (unpublished data), we investigated the response of SkBF in glabrous and non-glabrous skin to acute graded exercise to a submaximal workload. We have indeed shown that the response of SkBF significantly differed in glabrous (finger pulp) and non-glabrous (volar forearm) skin during exercise as well as in the recovery period.

While SkBF and CVC decreased in glabrous skin during exercise, it started to rise already during exercise (at about 60% of V_{O2max}) in non-glabrous skin. The fall of CVC in glabrous skin is consistent with increased sympathetic tone during exercise reflected by a simultaneous increase in HR as well as MAP. Also, the typical oscillations of CVC in the pulp disappeared during exercise what is consistent with the finding of Saad *et al*. *(68)*. As non-glabrous areas receive vasoconstrictor and vasodilator fibers the increase of CVC might reflect the activation of vasodilator fibers in non-glabrous skin as soon as the threshold was reached, i.e. at a workload of 60% of V_{O2max}.

In the recovery, SkBF in non-glabrous skin subsequently returned to the baseline value whereas SkBF in glabrous skin increased and remained elevated during recovery. A similar trend of LDF increase in the pulp in the recovery from dynamic exercise was observed in the only available study performed by Medbo *et al*. *(52)*.

The results point to different mechanisms of vasomotor control in glabrous and non-glabrous parts during a thermoregulatory challenge of graded dynamic exercise, respectively. It seems that non-glabrous skin is most importantly involved in thermoregulation during exercise while the main role for heat elimination in response to short lasting exercise is overtaken by glabrous skin in the recovery to exercise.

Another issue to be examined is how the two skin sites behave during prolonged exercise of high intensity. It seems probable that SkBF remains elevated in non-glabrous areas as long as the internal temperature is higher from the threshold; this, in turn, depends on the heat produced, i.e. on the intensity and duration of exercise. As for the glabrous skin, it would be interesting to see if and when SkBF started to rise during prolonged exercise. Does SkBF increase due to withdrawal of the sympathetic vasoconstrictor tone or are there local factors, such as endothelium and local temperature that prevail and augment blood flow. Namely, sympathetic vasoconstrictor tone is increased by the central command throughout the body during exercise and it is questionable whether sympathetic outflow to periphery could be regulated selectively in different organs/regions *(71)*. In this light, complete withdrawal of the sympathetic vasoconstrictor activity in glabrous skin to augment SkBF seems less probable. The available data on this issue are scarce and inconsistent *(49, 71)*; thus, the question remains elusive.

Finally it should be mentioned here that the response of SkBF to exercise is altered in conditions such as endurance training *(24, 25, 54)*, high altitude (hypoxic) or heat acclimation *(53)*. Endurance training, for example, is supposed to elicit changes of the reactivity of autonomous nervous system, endothelium, endocrine status as well as structural adaptations that finally lead to a decrease in the threshold for active vasodilation and an altered sensitivity of the 'SkBF to core temperature' slope *(24, 25, 54, 72)*. The detailed elaboration of these adaptations of CVS is reviewed elsewhere (*24, 25, 35, 54)*.

CONCLUSION

SkBF is regulated by competing thermoregulatory and nonthermoregulatory reflexes. Dynamic exercise impacts skin blood flow through several modifications of the vasoconstrictor and active vasodilator system that serve to maintain heat balance of the body without compromising the perfusion of metabolically active tissues. Inputs from central thermoreceptors that sense core temperature and peripheral thermoreceptors that sense skin temperature finally relay to skin vessels to adjust CVC. CVC as well as sweating rate are increased to eliminate additional heat produced in the skeletal muscles during exercise and preserve thermal homeostasis. Due to different innervation, glabrous and non-glabrous skin behaves differently during exercise as well as in the recovery period. In glabrous skin, the initial vasoconstriction prevails, decreasing CVC whereas in non-glabrous skin, active vasodilation beyond the threshold increases CVC. The exact interplay of these mechanisms in modulating the response of SkBF has to be elucidated in further studies.

REFERENCES

1. ROWEL L B 1994 Human cardiovascular control. Oxford University Press, New York
2. JOHNSON J M 2010 Exercise in a hot environment: the skin circulation. *Scand J Med Sci Sport 20 (Suppl. 3)*: 29–39
3. KENNY G P, JOURNEAY W S 2010 Human thermoregulation: separating thermal and nonthermal effects on heat loss. *Frontiers Biosci 15*: 259-90
4. RODDIE I C 1983 Circulation to skin and adipose tissue. *In:* Shepherd J T, Geiger S R *(eds)* Handbook of Physiology. Bethesda, p 285-309
5. BRAVERMAN I M 1997 The cutaneous microcirculation: ultrastructure and microanatomical organization. *Microcirculation 4(3)*: 329-40
6. BRAVERMAN I M, KEH A, GOLDMINZ D 1990 Correlation of laser Doppler wave patterns with underlying microvascular anatomy. *J Invest Dermatol 95*: 283-286
7. BERGERSEN T K, HISDAL J, WALLØE L 1999 Perfusion of the human finger during cold-induced vasodilatation. *Am J Physiol 276 (Regulatory Integrative Comp Physiol 45)*: R731–R737
8. KELLOGG D L JR 2006 In vivo mechanisms of cutaneous vasodilation and vasoconstriction in humans during thermoregulatory challenges. *J Appl Physiol 100*: 1709–1718
9. CHARKOUDIAN N 2010 Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans. *J Appl Physiol 109*: 1221–1228
10. JOHNSON J M, KELLOGG D L JR 2010 Thermoregulatory and thermal control in the human cutaneous circulation. *Frontiers Biosci S2*: 825-53
11. CHARKOUDIAN N 2003 Skin Blood Flow in Adult Human Thermoregulation: How It Works, When it Does Not, and Why. *Mayo Clin Proc 78*: 603-612
12. KELLOGG D L JR, ZHAO J L, WU Y 2008 Neuronal nitric oxide synthase mechanisms in the cutaneous vasculature in humans in vivo. *J Physiol (London) 586*: 847-857
13. MINSON C T 2010 Thermal provocation to evaluate microvascular reactivity in human skin. *J Appl Physiol 109*: 1239-1246
14. DEMACHI K, YOSHIDA T, KUME M, TSUJI M, TSUNEOKA H 2013 The influence of internal and skin temperatures on active cutaneous vasodilation under different levels of exercise and ambient temperatures in humans. *Int J Biometeorol 57(4)*: 589-96
15. CRANDALL C G, STEPHENS D P, JOHNSON J M 1998 Muscle metaboreceptor modulation of cutaneous active vasodilation. *Med Sci Sports Exerc 30(4)*: 490-6
16. KONDO N, TOMINAGA H, SHIBASAKI M, AOKI K, KOGA S, NISHIYASU T 1999 Modulation of the thermoregulatory sweating response to mild hyperthermia during activation of the muscle metaboreflex in humans. *J Physiol 515(2)*: 591—598
17. SHIBASAKI M, SAKAI M, ODA M, CRANDALL C G 2004 Muscle mechanoreceptor modulation of sweat rate during recovery from moderate exercise. *J Appl Physiol 96*: 2115–2119
18. SPRANGER M D, SALA-MERCADO J A, COUTSOS M, KAUR J, STAYER D, AUGUSTYNIAK R A, O'LEARY D S 2013 Role of cardiac output versus peripheral vasoconstriction in mediating muscle etaboreflex pressor responses: dynamic exercise versus postexercise muscle ischemia. *Am J Physiol Regul Integr Comp Physiol 304*: R657–R663
19. MACK G W, CORDERO D, PETERS J 2001 Baroreceptor modulation of active cutaneous vasodilation during dynamic exercise in humans. *J Appl Physiol 90*: 1464-1473
20. NOSAKA S 1996 Modifications of Arterial Baroreflexes: Obligatory Roles in Cardiovascular Regulation in Stress and Poststress Recovery. *Jap J Physiol 46*: 271288
21. AOKI K, STEPHENS D P, SAAD A R, JOHNSON J M 2003 Cutaneous vasoconstrictor response to whole body skin cooling is altered by time of day. *J Appl Physiol 94*: 930–934
22. GAGNON D, KENNY G P 2012 Sex differences in thermoeffector responses during exercise at fixed requirements for heat loss. *J Appl Physiol 113*: 746–757
23. LIMBERG J K, ELDRIDGE M W, PROCTOR L T, SEBRANEK J J, SCHRAGE W G 2010 Alpha-adrenergic control of blood flow during exercise: effect of sex and menstrual phase. *J Appl Physiol 109*: 1360–1368
24. FRITZSCHE R G, COYLE E F 2000 Cutaneous blood flow during exercise is higher in endurance-trained humans. *J Appl Physiol 88*: 738–744
25. SIMMONS G H, WONG B J, HOLOWATZ L A, KENNEY W L 2011 Changes in the control of skin blood flow with exercise training: where do cutaneous vascular adaptations fit in? *Exp Physiol 96(9)*: 822–828
26. KLONIZAKIS M, WINTER E 2011 Effects of arm-cranking exercise in cutaneous microcirculation in older, sedentary people. *Microvasc Res 81(3)*: 331-336
27. METZLER-WILSON K, KELLIE L A, TOMC C, SIMPSON C, SAMMONS D, WILSON T E 2012 Differential vasodilatory responses to local heating in facial, glabrous and hairy skin. *Clin Physiol Funct Imaging 32*: 361–366
28. THORIN E, HUANG P L, FISHMAN M C, BEVAN J A 1998 Nitric oxide inhibits alpha2-adrenoceptor-mediated endothelium-dependent vasodilation. *Circ Res 82*: 1323–1329
29. SHIBASAKI M, LOW D A, DAVIS S L, CRANDALL C G 2008 Nitric oxide inhibits cutaneous vasoconstriction to exogenous norepinephrine. *J Appl Physiol 105(5)*: 1504-8
30. MCCORD G R, CRACOWSKI J L, MINSON C T 2006 Prostanoids contribute to cutaneous active vasodilation in humans. *Am J Physiol Regul Integr Comp Physiol 291*: R596–R602
31. KELLOGG D L JR, ZHAO J L, WU Y 2008 Endothelial nitric oxide synthase control mechanisms in the cutaneous vasculature of humans in vivo. *Am J Physiol Heart Circ Physiol 295:* H123–H129
32. LENASI H, ŠTRUCL M 2008 The effect of nitric oxide synthase and cyclooxygenase inhibition on cutaneous microvascular reactivity. *Eur J Appl Physiol 103(6)*: 719-26
33. SHEPHERD A P, OBERG P A *(eds)* 1990 Laser-Doppler blood flowmetry. Kluwer Academic Publishers, Boston. Dordrecht, London,
34. SERUP J, JEMEC G B E, GROVE G L *(eds)* 2006 Handbook of Noninvasive Methods and the Skin. CRC Taylor & Francis Group, Boca Raton, London, New York,
35. LENASI H 2011 Assessment of human skin microcirculation and its endothelial function using laser Doppler flowmetry. *In:* Erondu OF *(ed)* Medical Imaging. In-Tech, Rijeka, p 271-296
36. CAL K, ZAKOWIECKI D, STEFANOWSKA J 2010 Advanced tools for *in vivo* skin analysis. *Int J Dermatol 49*: 492-499
37. TREU C M, LUPI O, BOTTINO D A, BOUSKELA E 2011 Sidestream dark field imaging: the evolution of real-time visualization of cutaneous microcirculation and its potential application in dermatology. *Arch Dermatol Res 303*: 69-78
38. KERAMIDAS M E, MUSIZZA B, KOUNALAKIS S N, MEKJAVIC I B 2010 Enhancement of the cold-induced finger vasodilation response with exercise training. *Eur J Appl Physiol 109*: 133-140
39. MEKJAVIC I B, EIKEN O 2006 Contribution of thermal and nonthermal factors to the regulation of body temperature in humans. J Appl Physiol 100: 2065–2072
40. GONZALEZ-ALONSO J, CRANDALL C G JOHNSON J M 2008 The cardiovascular challenge of exercising in the heat. *J Physiol* 586(1): 45–53

41. GONZALEZ-ALONSO J 2012 Human thermoregulation and the cardiovascular system. *Exp Physiol 97(3):* 340–346
42. KONDO N, TAKANO S, AOKI K, SHIBASAKI M, TOMINAGA H, INOUE Y 1998 Regional differences in the effect of exercise intensity on thermoregulatory sweating and cutaneous vasodilation. *Acta Physiol Scand 164*: 71-78
43. JOURNEAY W S, REARDON F D, MARTIN C R, KENNY G P 2004 Control of cutaneous vascular conductance and sweating during recovery from dynamic exercise in humans. *J Appl Physiol 96*: 2207–2212
44. KELLOGG D L JR, JOHNSON J M, KOSIBA W A 1991 Control of internal temperature threshold for active cutaneous vasodilation by dynamic exercise. *J Appl Physiol 71*: 2476-82
45. KVERNMO H D, STEFANOVSKA A, KIRKEBOEN K A 2003 Enhanced endothelial activity reflected in cutaneous blood flow oscillations of athletes. *Eur J Appl Physiol 90*: 16-22
46. ROSSI M, SANTORO G, MAURIZIO S, CARPI A 2006 Spectral analysis of skin blood flowmotion before and after exercise in healthy trained subjects. *Int J Sports Med 27*: 540-545
47. WILKINS B W, MINSON C T, HALLIWILL J R 2004 Regional hemodynamics during postexercise hypotension. II. Cutaneous circulation. *J Appl Physiol 97:* 2071–2076
48. JOURNEAY W S, REARDON F D, MCINNIS N H, KENNY G P 2005 Nonthermoregulatory control of cutaneous vascular conductance and sweating during recovery from dynamic exercise in women. *J Appl Physiol 99*: 1816–1821
49. HALLIWILL J R, TAYLOR J A, ECKBERG D L 1996 Impaired sympathetic vascular regulation in humans after acute dynamic exercise. *J Physiol 495(1)*: 279-288
50. CARTER R III, WILSON T E, WATENPAUGH D E, SMITH M L, AND CRANDALL C G 2002 Effects of mode of exercise recovery on thermoregulatory and cardiovascular responses. *J Appl Physiol 93*: 1918–1924
51. CHARKOUDIAN N, HALLIWILL J R, MORGAN B J, EISENACH J H, JOYNER M J 2003 Influences of hydration on post-exercise cardiovascular control in humans. *J Physiol 552(2)*: 635–644
52. MEDBO J I, HISDAL J, STRANDEN E 2009 Blood fl ow in the brachial artery increases after intense cycling exercise. *Scandinavian Journal of Clinical & Laboratory Investigation 69 (7)*: 752–763
53. LORENZO S, MINSON C T 2010 Heat acclimation improves cutaneous vascular function and sweating in trained cyclists. *J Appl Physiol 109*: 1736-43
54. GREEN D J, SPENCE A, HALLIWILL J R, CABLE N T THIJSSEN D H J 2010 Exercise and vascular adaptation in asymptomatic humans. *Exp Physiol 96(2)*: 57–70
55. SHIBASAKI M, CRANDALL C G 2011 Mechanisms and controllers of eccrine sweating in humans. *Front Biosci (Schol Ed) 2*: 685–696
56. SAWKA M N, CHEUVRONT, S N, KENEFICK R W 2012 High skin temperature and hypohydration impair aerobic performance. *Exp Physiol 97(3):* 327–332
57. SHEPHARD R J, ASTRAND P O 1992 Endurance in Sport. Oxford Blackwell Scientific Publications, London, Edinburg, Boston
58. KENNEY W L, STANHEWICZ A E, BRUNING R S, ALEXANDER L M 2013 Blood pressure regulation III: what happens when one system must serve two masters: temperature and pressure regulation? *Eur J Appl Physiol*: [Epub ahead of print]
59. SAWKA M N, YOUNG A J, FRANCESCONI R P, MUZA S R, PANDOLF P R 1985 Thermoregulatory and blood responses during exercise at graded hypohydration levels. *J Appl Physiol 59*: 1394-1401
60. BUONO M J, LEE N V L, MILLER P W 2010 The relationship between exercise intensity and the sweat lactate excretion rate. *J Physiol Sci 60*: 103–107
61. BUONO M J, MARTHA S L, HEANEY J H 2009 Peripheral sweat gland function is improved with humid heat acclimation. *J Therm Biol 34*: 127–130
62. FRYE A J, KAMON E 1983 Sweating efficiency in acclimated men and women exercising in humid and dry heat. *J Appl Physiol Resp Environ Exerc Physiol 54*: 972–977
63. DERBYSHIRE P J, BARR H, DAVIS F, HIGSON S P J 2012 Lactate in human sweat: a critical review of research to the present day. *J Physiol Sci 62*: 429–440
64. PATTERSON M J, GALLOWAY S D R, NIMMO M A 2000 Variations in regional sweat composition in normal human males. *Exp Physiol 85*: 869–875
65. FRYE A J, KAMON E 1988 Response to dry heat of men and women with similar aerobic capacities. *J Appl Physiol Respirat Environ Exercise Physiol 50(1)*: 65-70
66. BUONO M J, SJOHOLM N T 1988 Effect of physical training on peripheral sweat production. *J Appl Physiol 65(2)*: 811-814
67. KENNY G P, MURRIN J E, JOURNEAY W S, REARDON F D 2006 Differences in the postexercise threshold for cutaneous active vasodilation between men and women. *Am J Physiol Regul Integr Comp Physiol 290*: R172–R179
68. SAAD A R, STEPHENS D P, BENNETT L T, CHARKOUDIAN N, KOSIBA W A JOHNSON J M 2001 Influence of isometric exercise on blood flow and sweating in glaborous and nonglaborous human skin. *J Appl Physiol 91*: 2487-2492
69. YAMAZAKI F 2002 Vasomotor responses in glabrous and nonglabrous skin during sinusoidal exercise. *Med Sci Sports Exerc 34*: 767–772
70. YAMAZAKI F, SONE R 2006 Different vascular responses in glabrous and nonglabrous skin with incerasing core temperature during exercise. *Eur J Appl Physiol 97*: 582-590
71. VISSING S F, SCHERRER U, VICTOR R G 1994 Increase of sympathetic discharge to skeletal muscle but not to skin during mild lower body negative pressure in humans. *J Physiol 481(1)*: 233-241
72. LENASI H, ŠTRUCL M 2004 Effect of Regular Physical Training on Cutaneous Microvascular Reactivity. *Med Sci Sports Exerc 36(4)*: 606–612