

## Human thermoregulation: separating thermal and nonthermal effects on heat loss

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### 1. ABSTRACT

Human thermoregulatory control during heat stress has been studied at rest, during exercise and more recently during exercise recovery. Heat balance in the body is maintained by changes in the rate of heat loss via adjustments in skin blood flow and sweating. Independent of thermal control, the actions of nonthermal factors have important consequences in the control of heat loss responses during and following exercise. While the effect of these nonthermal factors is largely considered to be an inhibitory or excitatory stimulus which displaces the set-point about which temperature is regulated, their effects on human thermoregulatory control are far reaching. Many factors can affect the relative contribution of thermal and nonthermal influences to heat balance including exercise intensity, hemodynamic status, and the level of hyperthermia imposed. This review will characterize the physiological responses associated with heat stress and discuss the thermal and nonthermal influences on sweating and skin blood flow in humans. Further, recent calorimetric evidence for the understanding of thermal and nonthermal contributions to human heat balance will also be discussed.

### 2. INTRODUCTION

Heat balance in humans is maintained at near constant levels through the adjustment of physiological mechanisms designed to attain a balance between the heat produced within the body and the heat lost to the environment. Heat balance is easily disturbed during changes in metabolic heat production due to physical activity and/or exposure to a warmer environment. Under such conditions, elevations of skin blood flow and sweating occur via a hypothalamic negative feedback loop to maintain an enhanced rate of dry and evaporative heat loss. Inherent to this response is the concept of a thermoregulatory set-point or criterion body temperature. This is maintained by a thermostatic influence which drives powerful and highly developed behavioral and autonomic thermoregulatory responses in humans. Indeed, it is generally thought that the activation of autonomic thermoeffector activity is primarily governed by the thermal stimulation of central and peripheral sensors. However, independent of thermal control, nonthermal factors have an unequivocal influence on autonomic thermoregulatory responses in humans. This chapter

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provides an overview of the thermal and nonthermal influences on temperature regulation during exercise-related heat stress, with emphasis on the postexercise recovery period. For a more comprehensive discussion of the physiological control of human thermoregulation, the reader is referred to reviews by Cabanac (1) and Boulant (2).

### 3. OVERVIEW OF SKIN BLOOD FLOW CONTROL

The regulation of the cutaneous circulation is a major effector response of human thermoregulation. During periods of heat stress, elevations in core and skin temperature lead to reflex increases in skin blood flow (3). In thermally neutral environments, skin receives ~500 ml or 5-10 % of cardiac output, whereas in conditions of heat stress, up to 8 liters per minute or 50-70 % of cardiac output can be shifted to the skin (4-6). Thus, the thermoregulatory reflex adjustments in skin blood flow during heat exposure and/or exercise can impose a significant cardiovascular challenge.

Cutaneous arterioles are under tonic control of sympathetic vasoconstrictor fibers. They are also regulated by a unique vasodilator system, which is responsible for 80 to 95% of the total increase in skin blood flow during heat stress (5, 7). Additionally, vasoconstrictor reflexes have been shown to be reduced under conditions of passive hyperthermia (8, 9). For the purposes of describing the control of skin blood flow, the skin surface can be divided into two regions: 1) acral or glabrous (hands, feet, nose, and ears) and 2) non-acral or non-glabrous (head, limbs, and trunk). In acral regions, cutaneous arterioles are innervated only through noradrenergic sympathetic nerves (3, 10, 11). Thus, it follows that all thermal and nonthermal reflexes in the acral skin regions are mediated by adjustments in active vasoconstrictor tone. In contrast, non-acral areas contain a much more complex system for controlling cutaneous blood flow. Efferent neural control of skin blood flow to these areas is accomplished via two sympathetic neural pathways: a noradrenergic vasoconstrictor system (both  $\alpha_1$ - and  $\alpha_2$ -receptors) and a separate cholinergic active vasodilator system still under investigation (7, 12-15). It is the active vasodilator system that can increase skin blood flow by 80-95% under heat stress conditions (7). Additionally, both glabrous and non-glabrous regions of human skin are affected by local temperature, along with cellular and molecular factors (7, 16). At a higher level of control, however, the efferent outflow of information to the cutaneous neuronal synapses is governed by many thermal and nonthermal factors which influence the local circulation.

Anatomically, the glabrous and non-glabrous vascular beds have some inherent differences in addition to their varied innervation. Glabrous skin has a large number of arteriovenous anastomoses which can create large changes in blood flow in these portions of skin (17, 18). This anatomy is in stark contrast to non-glabrous skin where very few A-V anastomoses exist (7).

The amount of blood flow supplied to a given area of skin is mediated by two factors: 1) local factors

such as effects of local temperature on vascular tone and pressure responses, and 2) reflex controls related to internal metabolic heat production. A local factor that affects cutaneous circulation is a direct heating of the blood vessels themselves; however, the mechanisms for the vascular effects of local temperature are not yet well defined (19, 20). As stated by Johnson *et al.* (3), local cooling potentiates and heating weakens, the contractile response of vascular smooth muscle to norepinephrine and other constrictor agonists, apparently by changing the affinity of  $\alpha_2$ -adrenergic receptors. Research examining the cutaneous vascular responses to local heating and cooling indicates a prominent role for postjunctional  $\alpha_2$ -adrenoreceptors (12). Local cooling has been shown to enhance the affinity of  $\alpha_2$ -adrenoreceptors for norepinephrine and depress the function of other elements involved in vascular smooth muscle function. Conversely, the process of local heating is known to induce nitric oxide release which contributes to local thermal vasodilation (21, 22). The effect of local heating on skin blood flow is complex and can also be influenced by the magnitude and rate of heating as well as by the release of substances which can stimulate channels that are sensitive to capsaicin (20, 23, 24). For a detailed examination of local neuronal and biochemical control of the cutaneous circulation, please see other reviews (16, 25, 26).

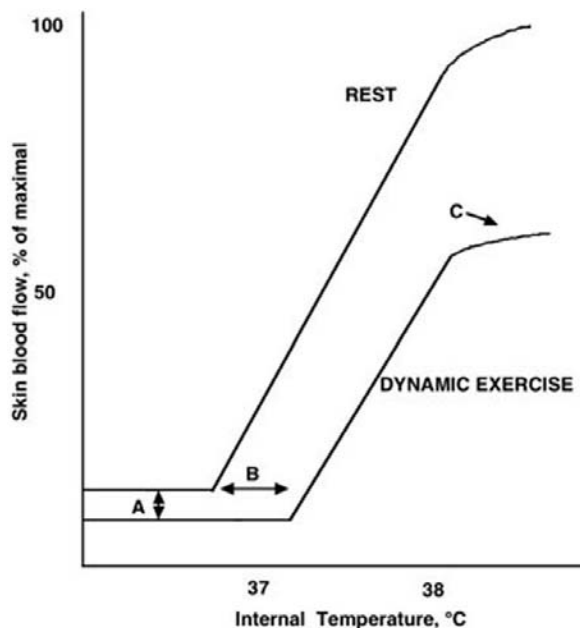
### 4. THERMAL FACTORS INFLUENCING SKIN BLOOD FLOW

The primary mechanism for stimulating heat loss responses of skin blood flow and sweating is that of the hypothalamic feedback circuit which receives an integrated signal from core and skin temperature (27). The thermally responsive control center of the brain is located in the preoptic area of the hypothalamus. It receives integrated information from skin and core temperatures to alter heat dissipation responses accordingly (28). This has been the generally accepted control system of the human thermoregulatory apparatus for many years.

The thermoregulatory apparatus can respond to a wide range of temperatures to cause varying increases in the cutaneous circulation. It also serves to provide an avenue for heat loss even at rest with heat loss of 80-90 kcal/h under thermoneutral conditions (7). This level of heat loss approximates basal metabolic rate and can occur at skin blood flow rates of 250 ml/min.

When core and skin temperatures rise as a result of exogenous or endogenous heating the body must dissipate the heat that is gained. The onset of a significant increase in blood flow to the skin occurs at core temperature thresholds which are commonly measured in thermoregulatory studies. The sensitivity of the cutaneous circulation to elevations in core temperature is typically represented by the slope of the skin blood flow-core temperature relationship after the onset temperature threshold of the rise in skin blood flow (29). The study of this relationship has served as the basis for altered control of heat loss in the thermoregulatory literature. Thus, under heat stress conditions, a change in the level of skin blood

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**Figure 1.** Schematic description of the thermoregulatory control of skin blood flow as modified by moderately intense exercise. The relation of skin blood flow to internal temperature is affected, relative to resting conditions, in at least three ways by exercise: a vasoconstrictor response at the onset of dynamic exercise (A), an increase in the internal temperature threshold at which skin blood flow begins to increase (B), and a leveling off, or plateau, in skin blood flow above an internal temperature of 38°C at a level well below maximal (C). Exercise exerts these effects through the vasoconstrictor system for the initial vasoconstriction and through inhibiting the active vasodilator system for the increased threshold and for the plateau. At rest, the plateau only occurs as skin blood flow approaches maximal vasodilatation. Reproduced with permission from, ref 45.

flow at a certain core temperature can be attributed to: 1) a change in the threshold for vasodilation (delayed or augmented response); 2) a change in the sensitivity (slope) of the blood flow increase, or 3) both factors (26). The relative influence of core and skin temperatures has been the subject of many studies. Results indicate that increases in skin temperature are a less sensitive driver of cutaneous blood flow than a similar increase in core temperature, which is representative of blood temperature sensed by the hypothalamic neurons (30, 31).

Dynamic exercise results in the reflex activation of many thermoregulatory, circulatory and metabolic controls. As core temperature rises due to the exercise-induced heat load, increases in skin blood flow (radiative, conductive and convective heat loss) and sweat rate (evaporative heat loss) serve to promote heat dissipation. Superimposed on these processes are nonthermal reflexes such as mechanoreflexes, central command, metaboreflexes and baroreflexes which are at play due to the exercise stimulus (3, 32-34).

The commencement of dynamic exercise leads to an increase in the threshold for skin vasodilation relative to heating at rest (29, 35-37). The magnitude of the increase in threshold is influenced by ambient temperature (38), in addition to a graded effect of exercise intensity on the threshold (35, 36, 39, 40). It is thought that the increased threshold for skin vasodilation is due to an effect of exercise on the active vasodilatory response (39, 41). This observation is based on the measurement of identical exercise-induced shifts in the core temperature threshold at which cutaneous vasodilation is initiated in skin locally treated with or without bretylium tosylate. Mack *et al.* (41) reported that baroreceptors may have a prominent role in modulating this response as evidenced by their findings that baroreceptor unloading (induced by the application of -40 mmHg lower body negative pressure (LBNP) during exercise): 1) delayed the onset of skin vasodilation; and 2) limited peak cutaneous vascular conductance at vasodilator-only forearm skin sites (without  $\alpha$ -adrenergic vasoconstrictor activity) relative to untreated forearm skin sites (with intact  $\alpha$ -adrenergic vasoconstrictor activity).

Reflex adjustments in cutaneous circulation are largely influenced by the competing thermoregulatory and metabolic demands for blood flow which are manifested from the onset of exercise (Figure 1). However, the pattern of response differs when exercise is prolonged. Indeed, after the initial rise in skin blood flow due to a rise in core temperature, the skin demonstrates a plateau or steady-state level of blood flow, despite an elevated state of hyperthermia as evidenced by a sustained increase in core temperature (42-45). This plateau phase observed during exercise occurs at much lower levels than those elicited under passive heating (50-60% peak) (7). In an effort to address the mechanism by which the suppression of skin blood flow occurs with prolonged exercise, a number of studies examined this response using systemic blockade of  $\alpha_1$ - (46) and  $\alpha_2$ -adrenoreceptors (47) or local blockade of norepinephrine release with bretylium (43). These studies showed that the attenuated rise in skin blood flow at higher levels of core temperature during prolonged exercise is primarily related to a functional limit in active vasodilator activity rather than an increase in vasoconstrictor activity.

## 5. NONTHERMAL FACTORS INFLUENCING SKIN BLOOD FLOW

While nonthermal influences on sudomotor activity presented below are a relatively new focus, the interaction of nonthermal factors with the cutaneous circulation has been the subject of study for many years (48, 49). It is the complex competition between thermoregulatory drive and the need for cardiovascular balance which serves as a basis for our understanding of nonthermal influences on the cutaneous circulation (50). Changes in skin blood flow during exercise can be initiated centrally but they are also subject to nonthermoregulatory controls such as central command, baroreflexes, muscle mechanoreceptors and metaboreceptors (3, 32-34).

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### 5.1. Baroreceptors and skin blood flow under thermoneutral conditions

The most widely studied of the nonthermal reflexes is that of the baroreceptor response. The cutaneous circulation has been shown to be on the efferent arm of the baroreflex (3, 49) and, from a teleological standpoint, will play a role in hemodynamic control given the limits on the relative distribution of blood to the skin and the other organs during thermal stress. Even in the absence of heat stress the cutaneous circulation is subject to baroreceptor-mediated vasoconstrictor reflexes in response to orthostatic stress (51, 52). Thus, activation of the baroreflex can initiate sympathetic nerve-mediated vasoconstriction in the periphery and in particular in the cutaneous vascular beds.

Baroreceptors are small stretch-sensitive receptors located in the carotid sinus and aortic arch (arterial baroreceptors) as well as in the atria, ventricles and pulmonary vessels (cardiopulmonary baroreceptors). Impulses received by receptors in the aortic arch travel via the vagus nerve to the nucleus tractus solitarius (NTS) in the medulla while the carotid arch receptors act through the sinus nerve up to the glossopharyngeal nerve before being received by the nucleus tractus solitarius (53). Stimulation of the NTS (baroreceptor loading) causes a depressor effect whereby sympathetic nerve impulses to the peripheral blood vessels are inhibited.

The baroreceptor reflex is the body's primary reflex pathway for homeostatic control of blood pressure. Baroreceptor loading associated with an increase in mean arterial pressure triggers an increase in sympathetic activity and a decrease in parasympathetic activity. This brings about increases in heart rate, myocardial contractility and a decrease in vasoconstrictor tone. Conversely, baroreceptor unloading in response to a decrease in mean arterial pressure causes a reduction in NTS activity, leading to skin vasoconstriction and an increase in heart rate (54).

Lower body negative pressure is a commonly employed experimental method for studying baroreceptor control of the circulation (55). Application of LBNP at levels equal to -40 to -50 mmHg in the supine position has been shown to reduce cardiac filling pressure due to local blood pooling in the legs. The drop in filling pressure during this maneuver triggers a strong baroreflex-mediated vasoconstriction in skeletal muscle and skin (56). The degree of vasoconstriction which occurs with the activation of the baroreflex is proportional to the level of LBNP (57). Regional vasoconstriction during LBNP occurs because arterial pressure must be maintained by a fall in vascular conductance inasmuch as the fall in ventricular filling pressure restricts the ability to raise cardiac output (58). There is substantial research in agreement that baroreceptor unloading decreases skin blood flow (52, 59-61) and thus has stimulated more research on the implications of the reflex in human thermoregulation.

The application of lower body positive pressure (LBPP) leads to an increase in both central venous pressure and mean arterial pressure through an enhanced gradient for venous return (57). Nishiyasu *et al.* (62) examined the

cardiovascular responses to LBPP in the supine and seated resting conditions. Application of positive pressure to the lower limbs caused a dramatic increase in stroke volume in the upright position from resting to +25 mmHg. They also observed that stroke volume was maximized between +25 and +50 mmHg and declined at higher pressures. The decline in stroke volume at high levels of LBPP is thought to occur as a result of increased mean arterial pressure which leads to increased total peripheral resistance and thus an increase in end-diastolic volume (62). In the supine position stroke volume did not change significantly with the addition of LBPP. Early work by Bevergard *et al.* (63) using LBPP of 40 mmHg as a means of increasing venous return demonstrated reflex forearm vasodilation via cardiopulmonary baroreceptor loading. Meanwhile Shi *et al.* (64) found that the hemodynamic responses to progressive increases in LBPP while resting in a supine position may be as a result of two different stimuli. An initial stimulus of LBPP occurs between 0 and 20 Torr (1 Torr = 1 mmHg) and appears to be a result of translocation of blood volume from the lower body to the thorax. It was also found that LBPP above 20 mmHg increases blood flow to the forearm (64).

This also raises the idea that cardiopulmonary and/or arterial baroreceptor groups can contribute to changes in skin blood flow. For example, varying degrees of LBNP (65-67) or head-down tilt (<30 degrees) (67-72) can engage the cardiopulmonary baroreceptors and possibly the arterial baroreceptor groups. Thus, this can lead to selective engagement of the cardiopulmonary baroreceptors in order to study their control of the cutaneous circulation. Under resting conditions, the effect of mild cardiopulmonary baroreceptor engagement demonstrates very little effect (73). The percentage change observed under resting conditions, however, will obviously be less than the change in skin blood flow in hyperthermic conditions where skin blood flow is elevated.

Many of the studies have focused primarily on the role of arterial baroreceptor populations which can also lead to the activation of neuroendocrine responses in addition to the acute baroreflex responses (74-76). Norsk *et al.* (76) noted that unloading of arterial baroreceptors seems to be a prerequisite for inducing increases in plasma arginine vasopressin during low body negative pressure (LBNP). The release of such mediators may then confound the specific role of baroreceptors in control of the skin circulation. Vasopressin is a potent vasoconstrictor that is released to defend arterial pressure during low blood pressure and hemorrhage (77). This has been supported by many other investigations that have shown that selective unloading of cardiopulmonary baroreceptors during low levels of LBNP without changes in arterial pressure did not induce an increase in arginine vasopressin release (75, 78, 79).

### 5.2. Baroreflex control of skin blood flow during hyperthermia

Baroreflex modulation of skin blood flow could be manifested at the level of the cutaneous vasculature by: 1) via changes in local reflex responses and biochemical

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changes, or 2) through the modulation of efferent activity at the level of the hypothalamus and brainstem cardiovascular centers in the medulla. Alternatively, baroreflex control of the skin circulation could be the manifestation of the integrated input of thermal controls and other nonthermal reflexes. Reports consistently demonstrate that loading and unloading manipulation of the baroreceptor reflex during passive heating at rest can decrease or increase the core temperature threshold at which blood flow begins to rise significantly (29, 60, 80). Extensive studies have examined the interrelationship of baroreceptor activity and skin blood flow control as a function of exogenously and endogenously induced hyperthermia as reviewed recently by Crandall (81).

The capacity of nonthermal baroreceptor reflexes to override thermoregulatory input, such as during hyperthermia, is critical to maintain blood pressure. However, this can significantly compromise heat loss. This is a reasonable linkage given that there is some hypothalamic control over baroreflex function (82). When the cardiovascular reflexes are overwhelmed by the demand for circulation to the skin and other organs, such as during prolonged exposure to hot ambient conditions and/or exercise in the heat, syncope may ensue. Studies show that when humans are heated to moderate levels of hyperthermia (core temperature  $<39.5^{\circ}\text{C}$ ), the vasoconstrictor function is maintained when an orthostatic stress is introduced (49, 50, 61, 83, 84). It is thought that the baroreflex exerts its action via the withdrawal of active vasodilator activity (60), however more recent work has also implicated altered vasoconstrictor responsiveness under whole-body heating conditions (8, 81). Whether this capacity exists at severe levels ( $>39.5^{\circ}\text{C}$ ) of passive hyperthermia is not yet known.

### 5.3. Central command

When examining the role of central command on the cutaneous circulation, it is important to note its concurrent impact on the cardiorespiratory system. Central command signals arise from the higher brain centers and descend in close proximity to the cardiorespiratory centers of the medulla. While there are many areas of the brain implicated in motor function, the area thought to have a significant effect on the circulatory and respiratory centers is the pre-motor cortex component of the cerebral cortex. This area is associated with the generation of motor signals in voluntary movement. The significance of the pre-motor cortex is that it projects into the medullary reticular formation, which is one of the areas involved in outflow controlling cardiorespiratory activity (85).

According to Rowell (86), the central hypothesis of central command is that it acts through cortical and motor systems “to set the basic patterns of effector activity which are in turn modulated by baroreceptors, muscle mechanoreceptors and muscle chemoreceptors as error signals may develop”. While the evidence that central command generates effector activity is plentiful, the mechanisms by which the patterns of nerve activity are modulated remain less clear. Moreover, deciphering the role of these signals in the regulation of heat loss responses can prove difficult.

Shibasaki *et al.* (87) evaluated the effect of central command on skin blood flow by using a partial neuromuscular blockade technique through the use of cisatracurium. Cisatracurium is a non-depolarizing muscle relaxant which blocks action potential transmission at the myoneural junction by binding with cholinergic receptor sites. As a result of the pharmacologic blockade experiments it was demonstrated that central command plays a role in the observed decrease in cutaneous vascular conductance during isometric hand grip (IHG) exercise in heat stressed test subjects. They found that central command, as well as metaboreceptors, contributed to the skin blood flow responses during heat stress. The passively induced heat stress in this study was typified by a  $\sim 1^{\circ}\text{C}$  rise in core temperature (as measured by ingestible telemetric pill) which is in keeping with the bulk of the literature on nonthermal control mechanisms being studied under moderate hyperthermia conditions ( $<39.5^{\circ}\text{C}$ ). This work extends upon the previous observations by Crandall *et al.* (88, 89) and Saad *et al.* (18) who reported that, while under normothermic conditions, IHG exercise does not alter skin blood flow in non-glabrous skin. Subjects under heat stress, however, exhibited vasoconstriction due to a withdrawal of active vasodilatory activity.

### 5.4. Metaboreceptors

Metaboreceptors are another nonthermal influence on the cutaneous circulation. Their role tends to be best studied using the ischemic IHG exercise technique. Metaboreceptors are chemosensitive afferents that respond to metabolic products in muscle and can influence control of the circulation (90). A study by Kondo *et al.* (91) examined the effect of metaboreceptor stimulation on the cutaneous circulation during passive hyperthermia and concluded that the muscle metaboreflex did not affect skin blood flow under mild hyperthermic conditions. Contrasting results were published by Crandall *et al.* (89) where it was demonstrated that metaboreflex stimulation under hyperthermia resulted in a significantly reduced level of cutaneous vascular conductance from baseline. In the Crandall *et al.* (89) study, skin blood flow was reduced during muscle ischemia under hyperthermic conditions, despite adrenergic vasoconstrictor blockade with bretylium. It was concluded that the decrease in blood flow was due to altered cutaneous active vasodilation.

In another study by Kondo *et al.* (92) core temperature was different between bouts of ischemic IHG exercise and thus they observed less of a reduction in cutaneous blood flow in the second bout ( $37.84^{\circ}\text{C}$ ) relative to the moderately-heated conditions during the first bout ( $37.54^{\circ}\text{C}$ ). Core temperatures were different due to the continued passive heating of the participants between exercise bouts. They speculated that this may be due to varying degrees of active cutaneous vasodilation between the two levels of core temperature, suggesting that nonthermal factors can be suppressed with increasing levels of hyperthermia. This suggests that thermoregulatory drive on the active vasodilator system at greater core temperatures leads to a lesser inhibition of blood flow during the ischemic handgrip stimulus. Although few conclusions can be translated directly to skin blood flow

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under conditions of dynamic exercise at this phase of research, it appears that, under experimental conditions which employ the ischemic IHG exercise model, muscle metaboreceptors tend to reduce active vasodilation.

### 6. OVERVIEW OF ECCRINE SWEAT GLAND CONTROL

Surface heat loss is significantly enhanced by the evaporation of sweat. The large quantity of thermal energy removed from the body during evaporation of water from the skin renders this process extremely important in human thermoregulation. Heat loss by evaporation of water occurs via several routes that differ greatly in their net physiologic significance. Such heat loss occurs through the mucous membranes of the oral, nasal, and respiratory passages, by passive diffusion through the skin (insensible perspiration), and by sweating.

With the exception of the palms of the hands and soles of the feet, thermal sweat is produced by the approximately 2-4 million eccrine sweat glands located across almost the entire body surface. However, only approximately 5% of the sweat glands are active at one time, indicating the tremendous potential for sweat production.

Sweat glands are innervated solely by the sympathetic nervous system. They differ markedly from other sympathetic end organs because they are cholinergic rather than adrenergic. Furthermore, these glands actively secrete sweat only when stimulated via nerve impulses. In response to nerve impulses, acetylcholine is released from cholinergic sudomotor nerves and binds to muscarinic receptors on the eccrine sweat gland (93). This activates a complex exchange of electrolytes creating the hypotonic sweat. The volume of sweat secreted is proportional to the frequency of the efferent nerve impulses. This overall effect of the nervous system on sweat secretion is termed sudomotor activity.

Evaporation provides the major defense against overheating. The quantity of heat loss by vaporization of water (i.e., evaporation of sweat) depends on two factors: 1) the rate at which water is secreted by the sweat glands; and 2) the ability of the ambient environment to remove water vapor. If the air is dry and moving quickly, then heat loss by evaporation is limited only by the rate at which sweat can be secreted. Conversely, if the air is humid and still, then heat loss is restricted by the capacity of the surrounding air to remove water from the skin surface. With high humidity, the ambient vapor pressure approaches that of the moist skin, and evaporation greatly diminishes, despite an elevated sweat rate. Thus, water vapor pressure of the air is a major factor in determining evaporative heat loss.

### 7. THERMAL FACTORS INFLUENCING ECCRINE SWEATING

The evaporation of sweat from the body surface represents the most important thermoregulatory mechanism

for eliminating the excess heat liberated from the exercising muscles. The rate of sweat secretion varies markedly depending on environmental temperature and the rate of metabolic heat production. During exercise in the heat, the body can lose between 1.0-2.5 L of sweat per hour. Under severe heat stress, maximal sweat production can reach a total of 10-15 L of sweat per day, but only with adequate fluid replacement.

Sweat rate increases rapidly at the onset of exercise albeit regional variations in the time of onset have been reported (94-96). This response is relatively independent of the level of exercise (94, 97). The increase in sweating occurs almost concurrently with the increase in the rate of metabolic heat production associated with the energy liberated from the working muscles (98, 99). Kondo *et al.* (95) showed that recruitment of sweat glands was very fast, with near maximal recruitment being achieved in as little as 8 min of passive heat stress or exercise. Some earlier studies proposed that the rapid increase in the onset of sweating, in the absence of a measurable increase in skin or core temperature, indicated the possible existence of muscle thermoreceptors (100). This hypothesis was based on the observation that the rapid increase in sweat output was paralleled by a rapid increase in muscle temperature of the exercising legs by as much as 1.5°C within the first minute of exercise. Others have suggested that the exercise-induced sweating may indicate a nonthermal rather than a thermal component in its regulation (101). Indeed, as discussed later in this review, recent evidence supports the hypothesis that factors such as mechanoreceptors, metaboreceptors, baroreceptors, and central command are likely involved in the regulation of sweating. As exercise continues however, core and skin temperatures (thermal factors) are thought to be the primary stimulus for sweating. This is supported by the observation that sweat rate during leg exercise was similar during rest for the same level of core and mean skin temperatures (29, 102).

It is important to note that while the rate of secretion of sweat is almost immediate upon the start of exercise, there is a significant delay in the evaporation of the sweat accumulated on the skin surface resulting in an increase in core temperature. Saltin *et al.* (103) noted delays in the increase of evaporative heat loss of between 2 to 5 minutes for a range of exercise intensities (300-1650 kpm/min) and ambient conditions (10, 20 and 30°C). In parallel, measurement of whole-body heat loss by direct calorimetry demonstrates that the exponential increase in the rate of heat loss lags significantly behind that for the increase in the rate of heat production during exercise. This results in net body heat storage (98, 104-106) and a corresponding increase in core temperature.

Sweat rate increases linearly with an increase in the intensity of exercise (101, 107-111). Exercise intensity does not alter the onset threshold for sweating (35, 94) even in a hypohydrated state (97). Whereas some studies show that the sensitivity of the response (94, 97) is influenced by the intensity of exercise others report no effect (103). However, this discrepancy is likely due to regional

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differences in sweating activity (94-96). Kondo *et al.* (94) reported an increase in the sensitivity of sweating on the forehead with increasing workload whereas no changes were measured for the limbs (forearm and leg) and torso (chest and back).

There are large variations in the distribution of sweat glands across body segments (112). Segmental differences in sudomotor function have been reported during rest and exercise with regard to sweat gland densities, secretion rates, thermal sensitivity and sweating onset (102, 113-120). These differences have primarily been characterized by an enhanced sweating response in the torso as compared to the limbs. For example, Nadel *et al.* (102) observed a tendency for the back, chest, and abdomen to begin sweating sooner and at greater rates than the limbs. However, a significant degree of variability between subjects was measured. Factors such as physical fitness (121) and level of acclimation (119, 121, 122) have been shown to modify the response, albeit some studies showed no effect of acclimation (113). Even within segments, sweat output can be highly variable. Recent studies report a non-uniform sweat distribution in foot (123), head (124) and torso (124, 125). The differences appear to be more pronounced with greater levels of hyperthermia (124).

Sato and Dobson (126) surmised that regional differences in sweat rate may be the result of differences in the density of activated sweat glands, sweat output per gland, or a combination of both factors. They measured the number of active sweat glands using starch-iodine paper. Sweat volume was quantified by weighing the filter papers. Local responses of the forehead, upper back and anterior forearm were evaluated during exercise performed in the heat. They showed that regional variations in maximal sweating were primarily dependent on differences in the number of activated sweat glands. Maximal sweat rate was significantly higher on the forehead than on either the forearm or back. This was consistent with a greater density of sweat glands on the forehead relative to the forearm and back. In contrast, individual variations in the maximal sweating response were primarily the result of differences in the function of the sweat glands and not due to differences in the number of activated sweat glands. Takano *et al.* (120) reported that regional variations in sweating rate were attenuated with increasing levels of exercise (i.e., 20, 40 and 60% of  $VO_{2max}$ ). They observed a proportionally greater sweating activity in the limbs and head. In contrast, Kondo *et al.* (94) reported that the magnitude of increase in local sweat rate was generally similar across regions. They did however measure a proportionally greater increase in local forehead sweating.

Buono and Connolly (127) suggested that the increase in whole body sweating (calculated from the change in body weight over the course of the exercise bout) observed with higher intensity exercise (i.e., 25, 50 and 75% of  $VO_{2max}$ ) is primarily due to an increase in activated sweat glands (as determined by multiplying the average number of sweat glands for six body sites by the body surface area), without an increase in sweat gland output.

However, Kondo *et al.* (94) showed that the increase in the sweat rate involves both an increase in the number of activated sweat glands and increased sweat gland output at low intensity exercise (i.e., 35% of  $VO_{2max}$ ). At higher intensity exercise (i.e., 50 to 65%  $VO_{2max}$ ), increases in sweat rate are primarily dependent on an increase in sweat gland output. Regional differences in the patterns of changes in activated sweat glands and sweat gland output for all intensities of work were also observed. The discrepancy in the observed responses between studies is likely due to differences in measurement protocol which includes the time during which the number of activated sweat glands was measured and the method used to calculate sweat gland output.

Sweat rate has been shown to increase during IHG exercise (128-131). However, unlike dynamic exercise, increases in sweat rate during brief static exercise generally occur without changes in core or skin temperature (91, 132). Under these conditions, changes in sweat rate are thought to be primarily associated with nonthermal factors. While local sweat rate in glabrous skin (e.g. palm) increases abruptly at the onset of static exercise and reaches a plateau, there is a delay in onset for non-glabrous skin (91, 132), albeit the delay is reduced with increasing intensity of exercise [i.e., 15.5 s at 30% of the maximal voluntary contraction (MVC) versus 10.8 and 8.8 s for 45 and 60% of MVC] (132). Furthermore, sweat rate increases progressively during the exercise (132) and the rate of increase is greater with higher intensity exercise (132).

The magnitude of increase in sweat rate in non-glabrous skin during IHG exercise is dependent on the level of thermal input (88, 92). Crandall *et al.* (88) reported no increase in forearm sweat rate when light isometric hand grip exercise (3 minutes at 30% of MVC) was performed in a normothermic state. Nevertheless, a marked increase in sweat rate was recorded when the exercise was performed in a mild hyperthermic state during which time sweating had already been activated and core temperature was significantly elevated (0.42°C) above baseline resting. However, the response was unchanged at higher levels of hyperthermia (core temperature of 0.56°C above baseline resting values). After sweating had been activated by passive heating, Kondo *et al.* (88, 92) also reported a diminished elevation in sweating response when moderate intensity static exercise (1 minute at 50% of MVC) was performed at increasing levels of hyperthermia. Thus, it appears that the relative influence of nonthermal stimulation in the control of sweating from non-glabrous skin is dependent on the level of thermal input and this response can be suppressed by sufficient hyperthermia.

As shown by Kondo *et al.* (132), local sweat rate is affected by the intensity of the IHG exercise in mild hyperthermic conditions (range in core temperature for all conditions: 37.14 to 37.16°C). They observed a significant increase in local forearm sweat rate during 1 minute of handgrip exercise performed at 30, 45 and 60% of MVC, but not at 15% of MVC. The increase in sweat rate on the forearm was not significantly different at 45 and 60% of

## Thermal and nonthermal influences on thermoregulation

MVC. More recently, Kondo *et al.* (133) examined the relative contribution of activated sweat glands and sweat gland output to sweating during sustained static exercise. They reported a comparable exercise intensity-dependent increase in local forearm sweat rate (1 minute at 20, 35 and 50% of MVC). They showed that the exercise intensity-related increase in sweat rate occurred as a result of a greater number of activated sweat glands rather than an increase in sweat gland output as previously observed during dynamic exercise. In *toto*, these studies reveal that sweating responses from non-glabrous skin during IHG exercise likely vary depending on the magnitude of the thermal input (88, 92) and the level of exercise (132).

### 8. NONTHERMAL INFLUENCES ON ECCRINE SWEATING

Following the onset of exercise the time taken to balance the differential rates of heat production and heat loss has been described as the thermal inertia (134) or temporal dissociation (135). In addition to thermal controllers of sweating and skin blood flow which may modify this response, factors unrelated to the elevation in core temperature (i.e. of nonthermal origin such as baroreceptors, mechanoreceptors, metaboreceptors, central command, etc.), but engaged during exercise, have been shown to modulate the rate of local sweating and skin blood flow (34, 41, 136, 137). Nonthermal factors may prolong the thermal inertia following the onset of exercise subsequent to the secondary influence on heat loss responses, thereby extending the time to achieve a stable core temperature (98, 104). Current research demonstrates that there are a number of possible nonthermal modifiers of sweating. These nonthermal influences are briefly reviewed in the following sections.

#### 8.1. Central command

The possible role of central command in the modulation of sweating activity was first highlighted in studies which examined the responses in skin and muscle sympathetic nerve activity during static exercise (128, 131, 138, 139). These studies showed that increases in skin and muscle sympathetic nerve activity occurred at the onset of exercise, however, the response pattern differed between them during and following exercise (128, 131, 138, 139).

Vissing *et al.* (131) and Saito *et al.* (128) reported that during exercise, central command may be the primary mechanism that triggers sympathetic activation to skin. This conclusion was based on the observation that exercise-induced increases in sympathetic outflow were not maintained during postexercise arterial occlusion of the forearm whereas muscle sympathetic nerve activity remained elevated. Vissing *et al.* (131) reported that the exercise-induced increase in skin sympathetic activity was paralleled by concomitant increases in electrodermal activity (an index of sudomotor activity) and skin blood flow. Of note, Saito *et al.* (128) also observed an increase in sweat rate of non-glabrous (foot volar) skin. In later work, Vissing and Hjortsø (138) studied skin sympathetic nerve activity during IHG exercise using partial neuromuscular blockade (vecuronium) to isolate the effects

of central command and eliminate or minimize input from muscle afferents including metaboreceptor influences (i.e., due to the reduced metabolic activity associated with the blockade-induced decrease in muscle tension development). Responses were compared at three exercise intensities: 10, 20 and 30% of MVC. As in previous studies, increases in skin sympathetic nerve activity preceded the onset of force development. The increases in skin sympathetic nerve activity were graded to the intensity of exercise although no increases were measured at 10% of MVC above control levels. Neural blockade resulted in reductions in force output equivalent to the force output measured during hand grip exercise performed at 10% of MVC before neural blockade. Despite the reduction in force output, skin sympathetic activity increased to levels similar to those observed during IHG exercise at 30% of MVC. Their findings provide neurophysiological evidence that central command may be implicated in the control of sudomotor activity. However, it is not possible to conclude from their findings that central command modulates thermal sweating as skin sympathetic nerve activity controls different end organ responses and local sweat rate was not measured concurrently.

The role of central command on local eccrine sweating was first examined by Kondo *et al.* (140). They examined local forearm and chest sweat rate during 2 minutes of assisted active and passive loadless single-legged cycling performed at 30 rpm and then at 60 rpm with an interval of 5 to 7 minutes between conditions. Prior to the start of exercise, subjects underwent whole-body heating until core temperature and sweat rate achieved steady state levels (within a period of 40-50 minutes). The mechanisms of the different exercise modalities are: during active loadless pedaling, skeletal muscle pump/mechanoreceptors and central command are activated, whereas during passive (assisted) cycling mechanoreceptors are stimulated without the involvement of central command (141-144). For both conditions, no change in skin or core temperature was observed. In contrast to passive cycling, active cycling was shown to result in a significantly greater sweat rate which was paralleled by a concomitant increase in heart rate supporting the role of central command in modulating sweat rate (143).

More recent work by Shibasaki and colleagues (145) confirmed the influence of central command on local sweating using IHG exercise (2 minutes at 35% of MVC) with and without partial neuromuscular blockade (using a curare derivative: cisatracurium). This protocol was used in view of previous work demonstrating that: 1) isometric exercise evokes a variety of physiological responses, including increases in heart rate, arterial pressure, and skin and muscle sympathetic nerve activity (131, 146-148); 2) increases in sweat rate during isometric handgrip exercise occur without changes in core and skin temperature (88); and, 3) neuromuscular blockade enhances central command during exercise resulting in a concomitantly greater increase in heart rate and blood pressure at a given work intensity (149). Trials were performed under normothermic, mild, and moderate hyperthermic conditions



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(0.5 and 1.0°C increase above baseline resting respectively). Neural blockade resulted in a significant reduction in MVC and force during the submaximal isometric handgrip exercise. However, despite this decrease, a greater sweat rate was measured in both the normothermic and the mild hyperthermic conditions. In contrast, sweat rate was reduced in the moderate hyperthermic state relative to control. While these observations provide additional evidence to support the role of central command as a possible modulator of sweating during exercise, it also demonstrates that the relative influence of central command is diminished or non-existent when body temperature is substantially elevated.

### 8.2. Metaboreceptors

The studies by Vissing *et al.* (131, 139) and Saito *et al.* (128) are some of the first studies to evaluate metaboreceptor stimulation of sweating under normothermic conditions. In these studies, a 2 minute handgrip exercise at 30% of MVC was followed by postexercise muscle ischemia induced by forearm vascular occlusion performed in the final 5 seconds (128) or immediately upon cessation of exercise (131). Occlusion of the forearm blood flow has been shown to result in a sustained elevation of blood pressure above resting levels (150, 151) and is considered an indicator that muscle metaboreflex activity is elevated. During the period of muscle ischemia, it is thought that the accumulation of metabolites within the muscle triggers chemosensitive afferents (group III and IV afferents) and reflexively raises arterial blood pressure (90). This maneuver maintains the stimulation of metaboreceptor muscle afferents and the reflex activation of muscle sympathetic nerve activity, while muscular relaxation eliminates both central command and the stimulation of mechanoreceptor muscle afferent (152-155). In these studies, end-exercise skin and muscle sympathetic activity were both significantly elevated above baseline levels. However, during and following the 2 minute forearm occlusion, skin sympathetic nerve activity decayed rapidly to baseline levels whereas muscle sympathetic nerve activity remained significantly elevated at end-exercise levels. This was paralleled by a rapid decrease in electrodermal function (an index of sudomotor changes) of non-glabrous skin (131, 139) and local sweat rate of glabrous skin (128). Saito *et al.* (128) reported a sustained increase in mean arterial pressure during occlusion indicating that muscle metaboreflex activity was indeed elevated. This suggests that thermoregulatory sweating is not modulated during activation of the muscle metaboreflex. Blood pressure data were not reported by Vissing *et al.* (131, 139) for these trials.

Subsequent work by Crandall *et al.* (89) showed that the influence of muscle metaboreceptors on local sweat rate is dependant of the level of hyperthermia. Under normothermic conditions local sweating during exercise, throughout the postexercise ischemia and recovery remained unchanged from baseline values. In contrast, when exercise was performed in a mild and moderately heat-stressed condition (an increase in core temperature of 0.55°C and 0.75°C above baseline resting respectively induced by whole-body warming), sweat rate increased

during the exercise from an elevated preexercise level and remained elevated throughout the exercise bout, the postexercise ischemia and the recovery period. During the postexercise ischemia, heart rate returned to preexercise levels whereas mean arterial pressure remained elevated. It is possible however that the increase in sweat rate may be attributed to thermal factors associated with the progressive increase in core temperature (156, 157) given that all three IHG exercise trials were performed consecutively in the same trial (i.e., resting under normothermic conditions followed by progressive heating). However, Kondo *et al.* (91) reported similar elevations in sweating during mild and moderate intensity IHG exercise and postexercise ischaemia performed under mild heat stress conditions (exposure to ambient temperature of 35°C). The environmental conditions were such as to induce sweating by increase in skin temperature without a marked change in core temperature. During circulatory occlusion after handgrip exercise at 30% of MVC for 120 seconds or at 45% of maximal voluntary contraction for 60 seconds, local sweating remained elevated despite the fact that core and skin temperature remained unchanged from baseline resting values. Noteworthy, occlusion alone (without prior exercise) and shorter duration exercise (60 seconds at 30% of MVC), did not result in an increased mean arterial pressure or local sweating response. This would indicate that for these two conditions, muscle metaboreceptors were either not activated (occlusion with no prior exercise) or not sufficiently activated during the shorter duration exercise to evoke a significant physiological response.

While the evidence suggests that the thermoregulatory sweating is modulated by muscle metaboreceptor activity, it is possible that under the experimental paradigm used to study the response, other non-thermal factors may be at play. Occlusion of the forearm blood flow results in a sustained elevation of blood pressure above resting levels. It is plausible therefore that the change in baroreceptor activity during the period of postexercise ischemia may have contributed to the sweating response. In order to evaluate the possible confounding influence of baroreceptor activity on local sweating during the post-IHG exercise ischemia, Shibasaki *et al.* (158) administered sodium nitroprusside intravenously during the postexercise ischaemia. The response was compared without the pharmacological manipulation of arterial pressure. Under these conditions, muscle metaboreceptors remain stimulated while baroreceptor drive is depressed to resting levels. They showed that sweat rate remained elevated during postexercise ischemia with the lowering of arterial blood pressure. A similar response was measured in both a normothermic and hypothermic (i.e., 0.5°C above baseline resting levels) state. Their findings indicate that activation of metaboreceptors and not baroreceptors modulates the sweating response during post-IHG exercise.

As reported by Crandall *et al.* (89), under normothermic conditions IHG exercise does not increase sweat rate. While Shibasaki *et al.* (158) findings of a sustained elevated sweating response during the postexercise ischaemia may appear to contradict Crandall's findings, the observed increase in local sweating during the

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2-min IHG exercise and postexercise ischaemia was measured with the administration of neostigmine. Neostigmine is an acetylcholinesterase inhibitor which is used to augment sweating. Shibasaki *et al.* (158) noted that the failure to observe a measurable increase in sudomotor activity and therefore sweat rate during IHG exercise under normothermic conditions may indicate that ‘insufficient quantities of acetylcholine were released from these nerves relative to the quantity necessary to overcome acetylcholine hydrolysis sufficient to evoke measurable sweating responses’. Indeed, Shibasaki *et al.* (158) observed an increase in local sweat rate at the neostigmine-treated site during the IHG exercise and subsequent postexercise ischaemia under normothermic conditions. No increase was observed in the untreated skin site. Moreover, regardless of whether mean arterial blood pressure remained elevated or was reduced (with the administration of sodium nitroprusside) during the postexercise ischaemia, local sweat rate remained elevated. Taken together, these studies provide strong evidence for metaboreceptors modulation of thermal sweating.

### 8.3. Baroreceptors

To date, there remains significant controversy regarding the role of baroreceptors in modulating thermal sweating. Studies demonstrate that skin sympathetic nerve recordings from sudomotor fibers show cardiac rhythmicity (159, 160). The sympathetic rhythms in the skin nerves were most evident when sudomotor activity was activated while the individual was exposed to a thermal stress. However, Bini *et al.* (159) noted that in contrast to muscle vasoconstrictor bursts, the latencies between heart beats and sudomotor bursts were not as stable as would be expected if the skin sympathetic nerve rhythmicity was generated by arterial baroreceptors.

Using postural manipulation (30° head-up tilt) and LBNP (-5 and -10 mmHg) to alter baroreceptor activity in passively heated individuals, Dodt *et al.* (161) measured a rapid reduction in skin sympathetic nerve activity and skin electrodermal activity (an index of sudomotor changes) during baroreceptor unloading, with both rapidly returning to control levels after cessation of LBNP. In contrast, Solack *et al.* (162) failed to measure a decrease in local sweat rate during the application of LBNP (-15 to -45 mmHg). While sweat rate did not decrease with the onset of LBNP, they did observe a 28% reduction in the forearm sweat rate-core temperature relationship. However, when LBNP was discontinued the slope remained unchanged in most participants. Given that the pattern of response was too slow to be explained by a neurally-mediated reflex, they surmised that the change in sweating thermosensitivity was likely a hormone-mediated response. However, the level of LBNP (-15 to -45 mmHg) was varied within and between experiments in order to elicit at least a 10% drop in forearm blood flow and to maintain systolic blood pressure near control levels. As such, differences in the relative contribution of low- and high-pressure baroreceptor activity may have influenced their findings (163).

Mack *et al.* (41, 164) extended upon previous work by demonstrating a baroreflex-mediated attenuation

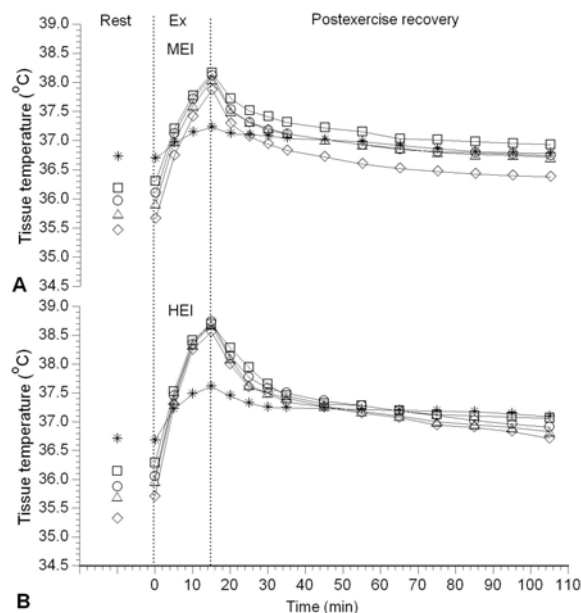
of sweating during exercise-induced heat stress. The application of LBNP during exercise resulted in an increase in the onset threshold for sweating. Of note, whereas in one study they recorded a decrease in sweating thermosensitivity, as measured by a decrease in the slope of the relationship between sweat rate and core temperature (164), no change in the sensitivity of the sweating response was measured in a subsequent study by the same group using the same experimental protocol (41). The discrepancy was attributed to an underestimation of the local chest sweat rate-core temperature relationship in the original study. Some subjects in the first study showed little or no sweating during the application of LBNP which may have influenced their results.

### 8.4. Considerations

A possible limitation of the aforementioned studies is the potentially confounding effects of non-baroreflex-mediated responses affecting skin sympathetic nerve activity during the perturbation used to change blood pressure. A number of factors such as mental stress, exercise, and hyperventilation have been shown to influence skin sympathetic nerve activity (165, 166). Skin sympathetic nerve activity is also very responsive to changes in core and skin temperatures (129, 131). Vissing *et al.* (167) suggested that rapid decay in skin sympathetic nerve activity observed during the application of LBNP was likely the result of factors unrelated to nonthermal baroreflex modulation but rather of thermal origin. This and other studies have recorded rapid decreases in mean skin temperature (and in particular of the lower body (162)) with the application of LBNP which may explain the reduction in skin sympathetic activity observed during the application of negative pressure to the lower limbs (41, 164, 167).

Wilson *et al.* (168) used pharmacological manipulation of blood pressure to assess baroreflex control of thermal sweating without the confounding influences of skin cooling that accompanies LBNP. All experimental trials were performed in a normothermic and hyperthermic state (core temperature between 0.6-1.0°C above baseline resting). Hyperthermia was achieved by whole-body heating using a liquid conditioned suit perfused with warm water (46°C) for 30-60 minutes. Bolus injections of sodium nitroprusside were initially administered to lower mean arterial pressure (~8 mmHg). This was followed by bolus infusions of phenylephrine to raise mean arterial pressure (~13 mmHg). A sub-group of subjects received steady-state intravenous infusions of sodium nitroprusside that were administered over 8 to 10-min in both the normothermic and heat-stressed condition. Throughout the protocol, skin sympathetic nerve activity was measured from the peroneal nerve. Sweat rate was measured via capacitance hygrometry within the area of innervation of the nerve fascicle. The pharmacological manipulation of arterial pressure did not elicit changes in skin sympathetic nerve activity and thermal sweating regardless of the level of heat stress. While these results suggest that skin sympathetic nerve activity and thermal sweating are not modulated by arterial baroreflexes, the influence of cardiopulmonary baroreceptors on these variables can not

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**Figure 2.** Mean changes in esophageal temperature (\*) and vastus medialis muscle temperature measured at 10 mm (□), 25 mm (○), 40 mm (△) and 55 mm (◇) from the deep femoral artery and femur, during resting, moderate (MEI), and high (HEI) intensity exercise and throughout 90 min of postexercise recovery. Reproduced with permission from, ref 175.

be discounted. Differences in the observed responses between this and other studies may be related to differences in the level of activation of low- and high-pressure baroreceptors with different maneuvers (i.e., pharmacological stimulation (169), LBNP (163, 170) and head-up tilt (170)).

In many of the aforementioned studies, the role of baroreceptors in the modulation of thermal sweating was evaluated during different levels of heat stress. Heat stress is known to cause progressive reductions in central venous pressure, right atrial mean pressure, and presumably central blood volume (171, 172). Wilson *et al.* (173) surmised that “the range through which cardiopulmonary baroreceptors would elicit a response (i.e., changes in skin sympathetic nerve activity and sweat rate) by head-up tilt would be minimized as central blood volume decreased during the heat stress”. As such, baroreceptors may be capable of modulating sweating differently under varying levels of thermal stress and may therefore explain the different responses observed between studies. To address this question, Wilson *et al.* (173) concurrently measured skin sympathetic nerve activity in the common peroneal nerve and local sweat rate during whole-body heating. Sweat rate was measured in the field of innervation and from two dorsal forearm sites: a neostigmine-treated and an untreated site. Neostigmine was administered to augment sweating at lower mean body temperatures. Multiple 30° head-up tilts were performed during whole-body heating, with tilting occurring every 10 min throughout the heat stress. Head-down tilt performed during whole-body heating had no

effect on skin sympathetic activity and local sweat rate at all sites. Whether baroreceptors are capable of modulating sweat rate, or the degree to which this occurs, remains an unanswered question.

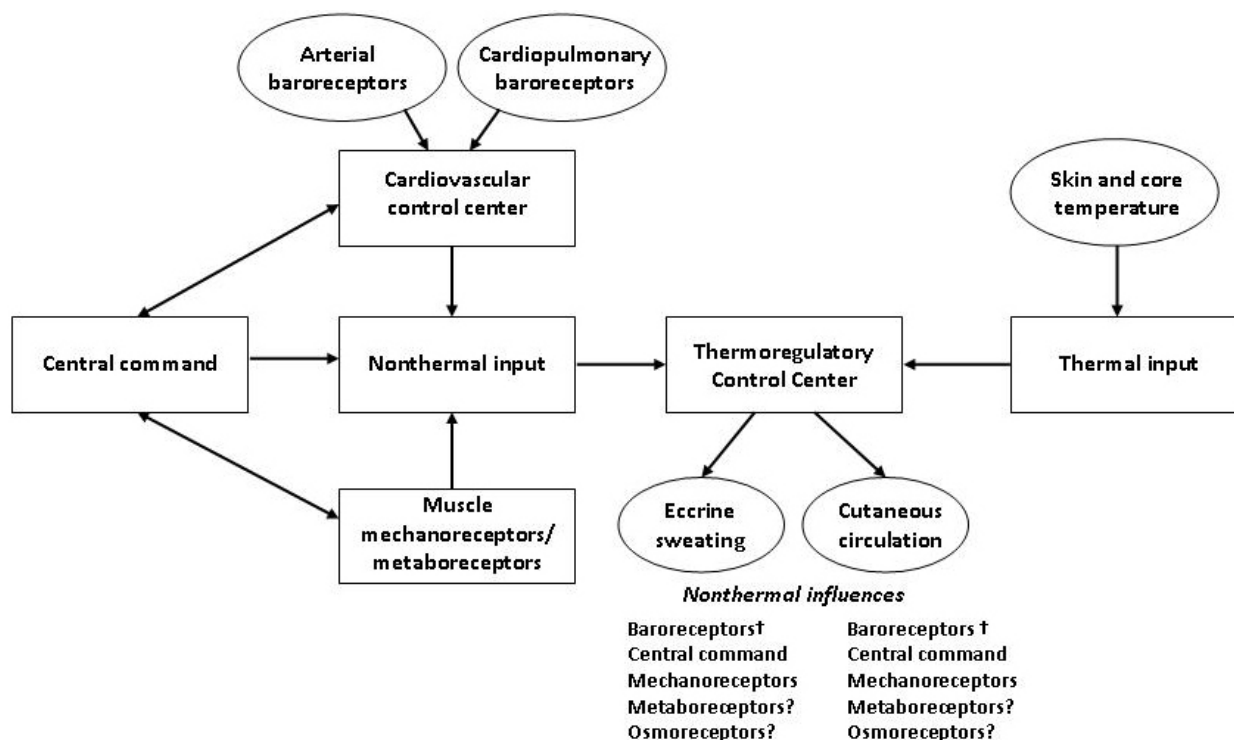
## 9. POSTEXERCISE THERMOREGULATION - OVERVIEW

There is increasing evidence that the thermoregulatory responses observed during the recovery period from dynamic exercise are inconsistent with those seen at rest under exogenous heating conditions or by endogenous heating during exercise. At the cessation of exercise, numerous studies have shown that local skin blood flow and sweating return to preexercise levels during the early stages of recovery despite sustained elevations in core and muscle temperature (174-183). This effect is greater during recovery after exercise of increasing intensity (175, 184) (Figure 2). As such, the association between local heat loss responses and core temperature appear to be different during exercise recovery.

This apparent perturbation in postexercise thermoregulatory control has been ascribed to nonthermal baroreceptor input associated with a postexercise hypotension response (174, 176, 180, 182, 185, 186). Some adjustments to the controlled “passive system” (i.e. the physical human body and the heat transfer phenomena occurring in it and at its surface (187)) will occur following exercise primarily due to changes in blood flow distribution. However, it is believed that the primary adjustment occurs in the controlling “active system” (188) such that the core temperature at onset of local sweating and cutaneous vasodilation is elevated (39, 176, 189).

Based on the known relationship between the cardiovascular system and heat dissipation, it follows that factors determining postexercise cardiovascular status may also attenuate postexercise heat loss responses, and consequently influence core temperature regulation. Studies have shown that a single bout of dynamic exercise elicits a persistent reduction in mean arterial pressure lasting nearly 2 hours (190) albeit the point of nadir appears to commence at approximately 15-20 minutes in both the supine (174) and upright seated postures (177). The magnitude of this decrease in mean arterial pressure is more pronounced and prolonged following exercise of increasing intensity (175, 184). Recent interpretation of data suggests that postexercise hypotension is due to a persistent rise in systemic vascular conductance that is not completely offset by increases in cardiac output (190). The combination of upright seated posture and removal of the skeletal muscle pump is thought to promote venous and muscle blood pooling (191). This reduces cardiac filling and unloads cardiopulmonary baroreceptors (190) and possibly arterial baroreceptors depending on the degree of hypotension exhibited in the upright posture. Halliwill *et al.* (190, 192) reported that baroreflex is reset to defend a lower blood pressure following exercise and sympathetic vasoconstrictor outflow is consequently reduced. Further, vascular responsiveness to sympathetic vasoconstrictor outflow is impaired so that vascular resistance is attenuated

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**Figure 3.** Schematic summary of nonthermal influences on postexercise heat loss responses. †, indicate a primary influence on heat loss responses during inactive recovery. The ‘?’ indicates that the influence listed remains to be studied.

for a given level of sympathetic nerve stimuli (193). The upright recovery posture would therefore tend to exacerbate venous and muscle pooling of warm blood during exercise recovery due to a higher hydrostatic pressure (190).

### 10. NONTHERMAL BAROREFLEX MODULATION OF POSTEXERCISE HEAT LOSS RESPONSES

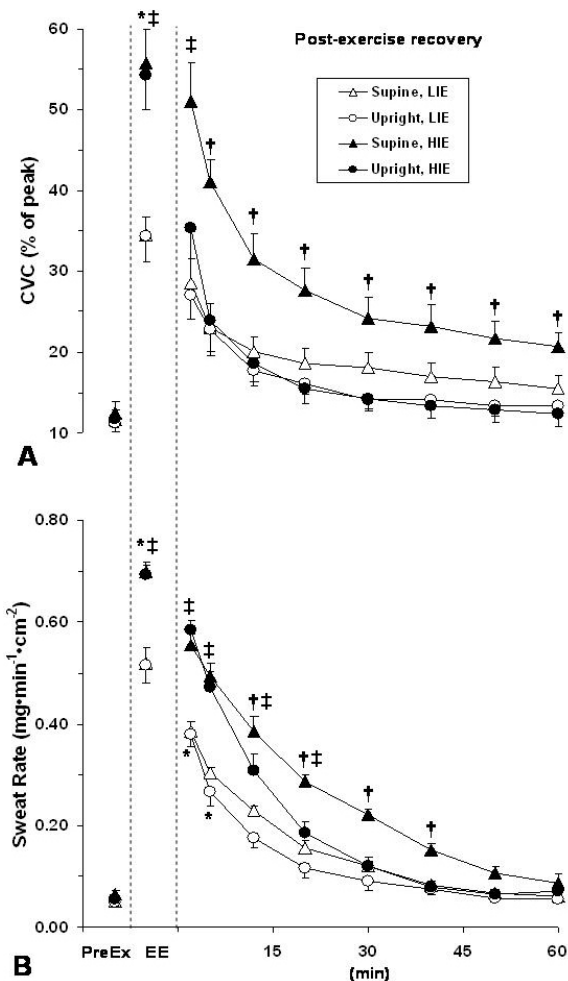
Nonthermal factors such as mechanoreceptors/muscle pump and central command described above have been shown to influence postexercise local sweat rate and skin blood flow (177, 194). Empirical evidence suggests however that baroreceptor afferent stimuli associated with postexercise hypotension is the primary overriding nonthermal influence responsible for the efferent modulation of local sweat rate and skin blood flow, and therefore core temperature response (175, 177, 183, 194-196). This hypothesis has evolved from the initial observation that a greater level of postexercise hypotension, induced by exercise of increasing intensity, results in a relative increase in the local onset of sweating (189) and skin vasodilation (39). This is accompanied by a concomitant increase in core and muscle temperature recovery time (175, 177, 182, 194). A summary of the nonthermal influences on postexercise heat loss response is presented in figure 3.

Taken together, these findings demonstrate a link between the observed postexercise cardiovascular changes and the altered thermal response thresholds for cutaneous vasodilation and eccrine sweating. This is further

supported by studies reporting that changes in hemodynamic response, such as an increase in stroke volume and mean arterial pressure, induced by the application of positive pressure to the lower limbs (+45mmHg) (177, 197), head-down tilt (183) or supine recovery (198) restores the altered thermal responses. Attenuating the baroreceptor unloading effect of exercise recovery in the early stages of recovery reverses the postexercise attenuation of skin blood flow and sweat rate and elicits a shorter core and muscle temperature recovery time.

Jackson and Kenny (197) showed that the postexercise increase in the onset threshold for sweating and skin blood flow is reversed with the application of +50 mmHg LBPP (197). Their findings demonstrate that LBPP, which is known to reverse postexercise hypotension and load baroreceptors, is capable of reversing the postexercise suppression of vasomotor and sudomotor activity. LBPP produces its effects via increased barometric pressure around the lower extremities. This leads to enhanced microvascular compression in the tissues and produces a pressure gradient that tends to increase central blood volume. With the application of sufficient barometric pressure to the lower extremities this technique may activate both cardiopulmonary and arterial baroreceptors (199). For example, a study showed that application of +45 mmHg of LBPP postexercise engaged both the cardiopulmonary and arterial baroreceptors (177). However, the involvement of 1) muscle metaboreflex, and 2) muscle mechanoreceptors; and/or 3) thermal factors

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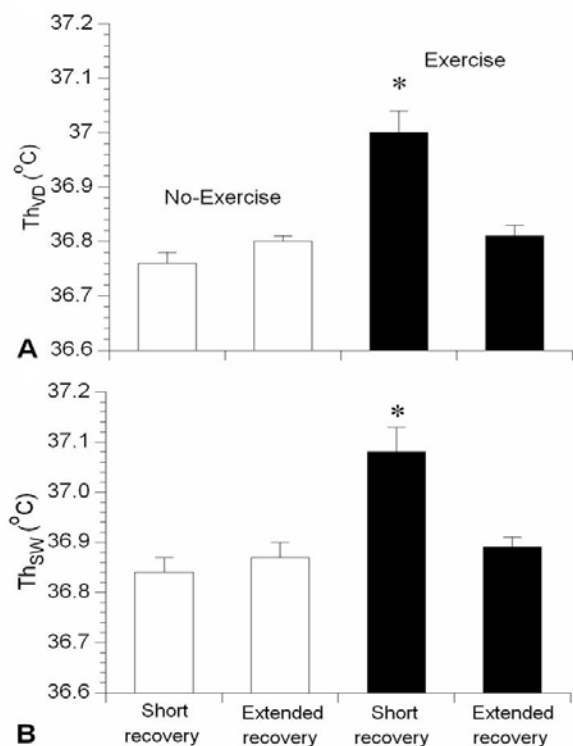


**Figure 4.** Effect of supine ( $\Delta$  and  $\blacktriangle$ ) and upright seated ( $\circ$  and  $\bullet$ ) recovery positions upon percentage of peak cutaneous vascular conductance (CVC) and local sweat rate (LSR) during 60 minutes of postexercise recovery following either low intensity exercise (LIE,  $\Delta$  and  $\circ$ ) or high intensity exercise (HIE,  $\blacktriangle$  and  $\bullet$ ). Significant difference between supine and upright seated positions within exercise intensity ( $\dagger$ ); low and high exercise intensity within the upright seated position ( $*$ ); and low and high exercise intensity within the supine position ( $\ddagger$ ). Values are means  $\pm$  SE for 7 female subjects. Reproduced with permission from, ref 198.

(associated with convective air exchange in the pressure chamber) (129, 131, 167) during LBPP application can not be discounted. Fu *et al.* (199) suggested that LBPP may activate mechanoreceptors particularly at pressures  $>20$  mmHg, whereas others have ruled out mechanoreceptor activation during LBPP (62). Convective airflow to the lower extremities may increase heat loss from the lower extremities which may account for the enhanced rate of core temperature decay (177).

Additional evidence for the role of cardiopulmonary and/or arterial baroreceptors in the modulation of postexercise heat loss responses is demonstrated by studies employing postural manipulation (181, 183, 198) to reverse the postexercise hypotension. McInnis *et al.* (183) showed that extended recovery from dynamic exercise in the  $15^\circ$  head-down tilt position attenuates the reduction in cutaneous vascular conductance and sweating when compared with the responses measured during recovery in the upright seated posture. This was paralleled by a concomitant increase the rate

of esophageal temperature decay. Recovery from exercise in a supine posture has been shown to result in a reflex bradycardia, increased stroke volume, and a lower total peripheral resistance compared with an upright recovery posture (200, 201). While Wilson *et al.* (8) studied the effect of inactive versus active recovery following supine cycling ergometry on thermal and cardiovascular responses, a recent study by Kenny *et al.* (198) examined the effect of a supine recovery relative to the upright seated exercise posture. Consistent with the findings using LBPP and  $15^\circ$  head-down tilt, supine recovery was shown to attenuate the postexercise reductions in mean arterial pressure, cutaneous vascular conductance, and sweat rate in a manner dependent directly on exercise intensity. Although cardiopulmonary baroreceptors were implicated following both low- (55% of  $\text{VO}_{2\text{max}}$ ) and high-intensity (85% of  $\text{VO}_{2\text{max}}$ ) exercise, they concluded that the postexercise attenuation of cutaneous vascular conductance and sweat rate is evident with the combined influence of arterial baroreceptors (Figure 4).



**Figure 5.** Mean ( $\pm$  SE) esophageal temperature threshold at the onset of cutaneous vasodilation (A,  $Th_{VD}$ ) and sweating (B,  $Th_{SW}$ ) for no-exercise and exercise measured during whole-body warming following a short (20-min) and extended (60-min) post-treatment resting recovery. Open bars, no-exercise treatment trials; solid bars, exercise treatment trials. Exercise resulted in significant increase in the thresholds for cutaneous vasodilation and sweating above both no-exercise resting trials when measured following a short recovery and was similarly elevated above the postexercise threshold value recorded following an extended recovery. \*  $p < 0.05$ . Reproduced with permission from, ref 195.

Kenny and Journeay (195) examined the time-line response of postexercise skin blood flow and sweating. Participants performed 15 minutes of moderate intensity exercise followed by either a 20 or 60 minute upright recovery period at which time subjects underwent whole-body heating to measure the onset and thermosensitivity of the sweating and skin blood flow response. A 20 minute recovery was chosen to maximize the magnitude of baroreceptor unloading whereas a 60 minute recovery was employed to ensure that mean arterial pressure was reestablished through the normal time-dependent reflex adjustments of hemodynamics that occur with prolonged recovery (190). Exercise resulted in an increase in the onset of skin vasodilation and sweating of  $0.24^{\circ}\text{C}$  and  $0.24^{\circ}\text{C}$  respectively above no-exercise during the early stages of recovery ( $<20$ -min). However, the postexercise increase in the onset threshold for sweating and skin vasodilation was reversed when recovery was long enough for natural restoration of mean arterial pressure to baseline resting

values (60-min) (Figure 5). Their findings suggest that, with extended recovery, cardiopulmonary and/or arterial baroreceptor unloading is likely negated, leading to no change in the observed thermal response thresholds.

### 11. THE RELATIVE CONTRIBUTION OF NONTHERMAL INPUT ON POSTEXERCISE HEAT LOSS RESPONSES

Despite the well-characterized influence of baroreceptor activity on postexercise thermoregulation, there remains a paucity of information regarding the contribution and interplay of other nonthermal stimuli on thermoregulatory effector responses. To address this, a number of studies have attempted to delineate the relative contribution of nonthermal stimuli such as central command, mechanoreceptors/skeletal muscle pump, and baroreceptors in modulating skin blood flow and sweating postexercise as a function of recovery mode in males (177, 181, 202-204) and females (181, 194). Cardiovascular responses to active, passive and inactive recovery were first studied by Carter *et al.* (141). Subsequently these recovery modes have been used to study the nonthermal influences on heat loss responses. Briefly, the mechanisms of the different recovery modalities are: 1) during active recovery (loadless pedaling) skeletal muscle pump/mechanoreceptors and central command are activated, 2) during passive cycling mechanoreceptors are stimulated without the involvement of central command (141-144), and; 3) during inactive recovery baroreceptors are primarily implicated. While baroreceptors are implicated in each recovery mode, it is believed that they are the primary nonthermal influence on skin blood flow and sweating in the inactive mode (177, 180, 194).

Carter *et al.* (203) evaluated the hypothesis that active recovery (unloaded cycling) would maintain the elevation in skin blood flow and sweating during the very early stages of exercise recovery (first 5 minutes of recovery) in the upright posture. They showed that cardiac output and stroke volume were significantly elevated relative to during inactive recovery. This was paralleled by a concomitant elevation in skin blood flow and sweating. Although core temperature remained significantly elevated above baseline resting values, no differences in core temperature response between conditions was observed. Of note however, mean arterial pressure decreased similarly during both inactive and active recovery to normal resting levels, indicating that baroreceptor loading status was unchanged. Wilson *et al.* (8) employed a similar study design using supine recovery to minimize the differences in central blood volume and therefore the magnitude of baroreceptor unloading compared with recovery in the upright position. Consistent with the findings of Carter *et al.* (203) they showed that sweat rate remains significantly elevated during active compared with inactive recovery. No differences were observed in cutaneous vascular conductance between conditions. Subsequent work by Shibasaki *et al.* (204) showed that muscle mechanoreceptor stimulation is capable of modulating local sweat rate but not cutaneous vascular conductance. In their study, participants underwent either a 10 minute passive recovery

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or no leg movement in the supine position. Passive cycling was achieved by a second person pedaling a tandem ergometer while the subject's legs passively moved. Taken together these studies suggest that while cutaneous vascular conductance is primarily influenced by baroreceptor loading status, sweat rate is influenced by other nonthermal factors including central command and/or muscle mechanoreceptors.

While these studies demonstrate that nonthermal stimuli can modulate the heat loss effector responses of skin blood flow and sweating differently in the postexercise recovery period, it is not possible to differentiate the relative contribution of each since only an active or passive recovery was performed in combination with an inactive recovery. Furthermore, these findings are limited to the first 5 to 10-min of recovery which is preceded by a light intensity exercise bout (60-65% of the individual's predicted maximal heart rate). Many of the cardiovascular and thermoregulatory adjustments occur after 5 minutes of recovery and the effects are more pronounced following greater intensity exercise bouts (175, 184). A recent study conducted by Journeay *et al.* (177) provided the first insight into the relative influence of nonthermal afferent stimuli during the transient decrease of blood pressure that occurs in the early- to mid-stages following acute exercise. They studied the separate effects of passive, active and inactive recovery on cardiovascular and thermoregulatory responses using an exercise paradigm which had previously been shown to elicit postexercise hypotension. Responses were compared over a 15 minute recovery period. In contrast to the findings of Carter *et al.* (203), they observed a marked separation of mean arterial responses between inactive and both passive and active recovery during the 15 minute recovery period with mean arterial pressure reduced below baseline values at the end of inactive recovery. This was paralleled by a concomitant reduction in both skin blood flow and sweating, although the fall in sweat rate during exercise recovery was dependent on each recovery mode. Sweat rate was greater during active recovery compared to passive recovery whereas inactive recovery was lower than either active or passive recoveries. Given that mean arterial pressure was greater during both passive and active recovery modes than during inactive recovery, these data suggest that differences in cutaneous vascular conductance may be predominantly due to differences in baroreceptor unloading and not factors attributed to central command. The different sweat rate responses observed between the three recovery modes confirm that factors such as central command and mechanoreceptors influence sweat rate. However, given the separation in mean arterial pressure, the possibility of baroreceptor influence cannot be discounted.

An important limitation to the interpretation of the findings obtained from the recovery mode studies relates to the use of core temperature as a surrogate measure of metabolic heat production. Most studies did not compare measurements of oxygen consumption between either active or passive and inactive recovery modes. Rather, it was assumed that any elevations in metabolism during active or passive recovery relative to inactive

recovery were insufficient to produce changes in hypothalamic temperature (177, 194, 204) as evidenced by the similar core temperature between recovery modes. Consequently, previous studies have ruled out the possibility that elevations in heat production are responsible for the elevation in skin blood flow and sweating observed during a passive and/or recovery mode. However, the elevated metabolic heat production associated with an active or passive recovery may diminish any increase in potential for net heat loss when compared with inactive recovery as measured by core temperature (177, 194, 204) (Figure 6). A recent report concluded that a similar core temperature is possible at different levels of postexercise heat production (205).

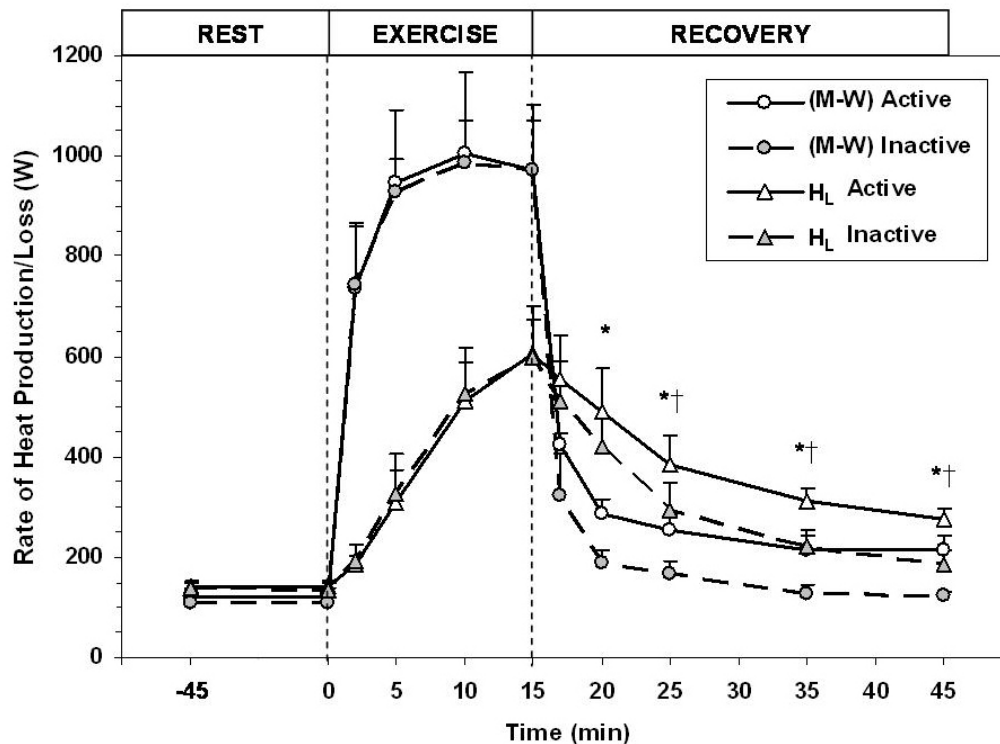
## 12. OTHER FACTORS

### 12.1. Level of hyperthermia

All of the aforementioned studies are based on individuals rendered only mildly hyperthermic (end-exercise core body temperature of 37.0-38.1°C). In exercise-induced hyperthermia (i.e., core body temperature > 38.5°C), elevated skin blood flow and sweating responses, combined with a higher cardiovascular strain, can lead to an even greater and more prolonged reduction in postexercise blood pressure in comparison with a lower heat stress state in males (206). However, it is well established that thermoregulation during heat stress is primarily achieved by initiation of thermoeffector mechanisms by the peripheral and central temperature sensors (102). Kondo *et al.* (92) reported that the level of hyperthermia may modify the level of nonthermal modulation of heat loss responses. A reduction in the effectiveness of nonthermal factors upon sweating and skin blood flow as measured during isometric handgrip exercise protocol was observed during moderate increases in core temperature (0.3-0.4°C). Similarly, Gagnon *et al.* (207) showed that in the presence of a greater thermal drive (as defined by an end-exercise core temperature of 39.5°C), the influence of nonthermal input upon postexercise heat loss was attenuated. This was evidenced as a delay in the manifestation of nonthermal influence. Specifically, the relative contribution of thermal factors to the regulation of cutaneous vascular conductance predominates over nonthermal factors in the first 10 minutes of recovery and up to 50 minutes postexercise for sweating (Figure 7). Thereafter, regulation of cutaneous vascular conductance and sweating was influenced primarily by muscle pump/mechanoreceptors and baroreceptors. Noteworthy, the augmented cardiovascular and heat loss responses were associated with an increased rate of core temperature decay during passive recovery relative to active recovery (shown in the statistical analyses by a significant interaction between recovery mode and recovery time).

### 12.2. Hydration status

It could be argued that differences in hydration status may in part explain the postexercise attenuation of heat loss responses. Hypohydration-mediated cardiovascular strain results primarily from reduced plasma volume (97, 208-210). Under hyperthermic conditions, this hypohydration-mediated cardiovascular strain can be



**Figure 6.** Mean whole-body calorimetry data for the rate of net total heat production (M-W) and rate of total heat loss ( $H_L$ ) for both inactive and active postexercise recoveries. Vertical dotted lines indicate onset and cessation of exercise. Error bars indicate standard deviation. Significant difference between recovery modes are indicated by asterisk (\*) for M-W and dagger (†) for  $H_L$ . Note that the differences in  $H_L$  are proportional to the differences in M-W. Reproduced with permission from, ref 205.

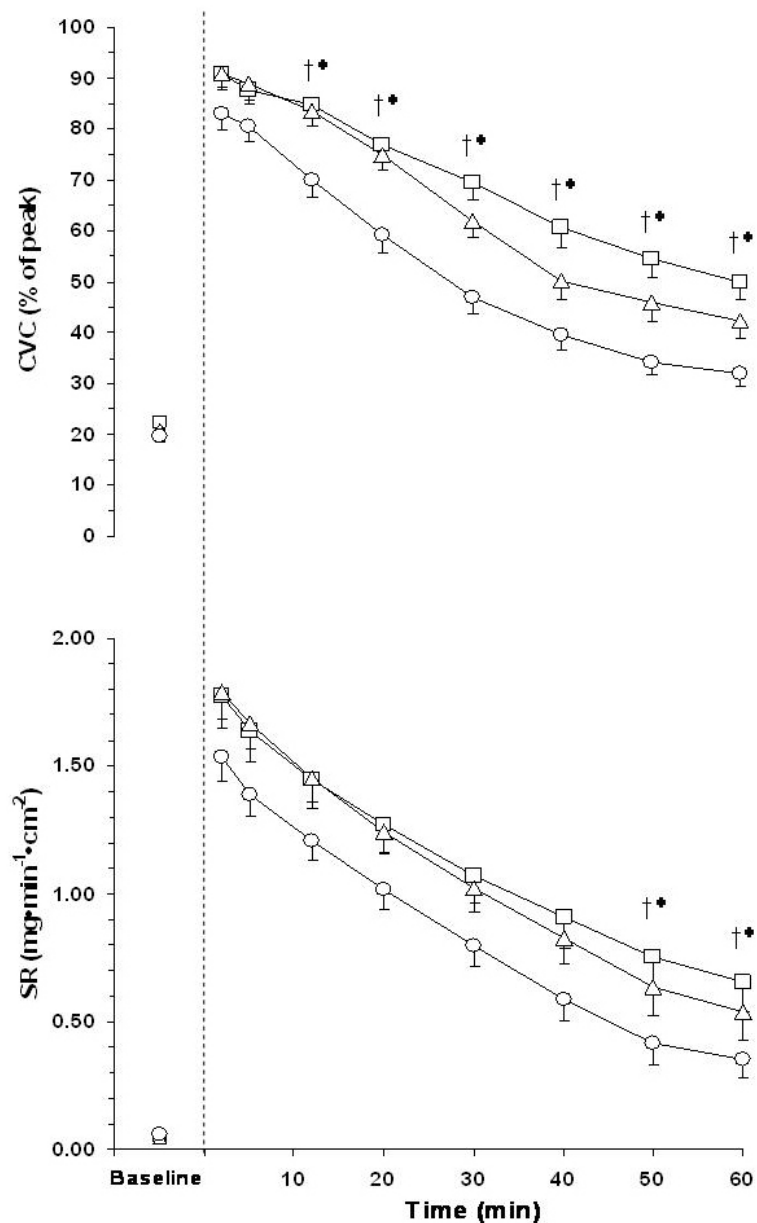
exacerbated due to redistribution of blood to warm skin (211). Prolonged exposure to a passive heat stress induces a pattern of cardiovascular and thermoregulatory changes similar to those induced by exercise (212). Passive hyperthermia alone (which is augmented by exercise and hypohydration) is reported to decrease cardiac vagal modulation of heart rate (213). Dehydration, which leads to blood hypovolemia and hyperosmolarity (214), is associated with an increased core temperature and heart rate during physical work in temperate (215, 216) or hot environments (210, 214). Sawka *et al.* (217) reported that with each 1% of dehydration there is a corresponding increase in core temperature of 0.1-0.2°C. They noted that the greater heat storage associated with dehydration is mediated by a decrease in whole-body dry and evaporative heat loss as evidenced by reductions in skin blood flow and local sweating responses. Studies show that hypohydration increases the onset threshold for local sweating and skin vasodilation (218) and that the magnitude of the response is dependent on the level of hypohydration (97). It is plausible, therefore, that the postexercise suppression of sweating and skin blood flow may be the result of, or at least accentuated by, relative hypohydration which may be exacerbated by the level of hyperthermia. However, it has been suggested that the experimental exercise paradigm employed to study postexercise thermal control (i.e., short duration ( $\leq 15$  min) of moderate-intensity exercise performed in a temperate environment with unrestricted pretrial and preexercise water) would not have caused dehydration to a level which

would have significantly compromised postexercise heat loss responses (39, 40, 176, 189, 219, 220). Montain and Coyle (208) for example demonstrated that 2 hours of dynamic exercise (65% of  $VO_{2max}$ ) in a warm environment (33°C) with no water intake resulted in a maximum weight loss of 4.2 kg. Thus, a 70-kg adult could potentially lose ~2.5% of water content per hour of heavy exercise in the heat owing primarily to water loss from sweating (221).

Carter and colleagues (222) evaluated the effects of hypohydration (4% body weight loss) on postexercise seated recovery in the heat (40°C). When the subjects initiated the hypohydration exercise-heat trial, they had been dehydrated ~15 hours before and had rested quietly in a temperate climate (24°C). It was shown during 45 minutes of exercise recovery while hypohydrated in the heat (40°C), seated heart rate and core temperature remained elevated relative to the euhydration condition. Charkoudian *et al.* (223) studied the influence of hypohydration (1.6% body mass loss) on cardiovascular control after exercise-heat stress. Pharmacological manipulation (nitroprusside and phenylephrine) of blood pressure was used to evoke acute rapid changes in blood pressure responses. They observed that when subjects were hypohydrated by 1.6% body weight loss, cardiac baroreceptor sensitivity was reduced compared to when euhydrated after a 90 minute exercise recovery period. Restoration of plasma volume by saline infusion did not



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**Figure 7.** Effect of recovery mode upon percentage of peak cutaneous vascular conductance (CVC) and Sweat rate (SR) during 60-min of postexercise recovery following exercise-induced hyperthermia. Significant difference between active and inactive recovery (\*); and passive and inactive recovery (†). Values are means  $\pm$  SE for 9 males and 9 females. N.B. Statistical analyses performed upon changes from preexercise baseline rest. Reproduced with permission from, ref 207.

immediately restore these physiological responses (223). Their findings suggest that blood pressure regulation may be profoundly influenced by thermal stress via altered baroreceptor mechanisms after exercise.

### 12.3. Sex-related differences

The majority of the studies investigating the postexercise changes in core temperature and mean arterial pressure have been conducted in males. A growing number of studies conclude that the integration of the various mechanisms and pathways modulating the pattern of postexercise hemodynamics is influenced by sex (182,

224). This is based on the observation of postexercise differences in vascular conductance and arterial pressure between males and females. Studies show that while the temporal pattern of postexercise hypotension is similar in both sexes, females experience greater reductions of postexercise blood pressure relative to males following moderate intensity exercise (40-70% of  $VO_{2max}$ ) ranging in duration from 5 to 70 minutes duration (40, 182, 224, 225). Of note, Senitko *et al.* (226) reported no difference in postexercise mean arterial pressure between sexes following 60 min of moderate intensity (60% of  $VO_{2peak}$ ) upright seated cycling. However, in this particularly study,

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the majority of the recovery period was spent in the supine position with participants only in a head-up recovery position for a 5 minute period, after ~45 minutes of recovery.

There have been many reports of reduced tolerance of orthostatic challenge in females compared with males (227-230). Carter *et al.* (224) suggested that females may be more susceptible to postexercise hypotension based on the observation that females had a greater reduction in mean arterial pressure and less compensatory vasoconstriction than males. Christou *et al.* (231) observed that females have less effective baroreflex buffering of arterial blood pressure as compared to males. The apparent effect of recovery posture upon the sex-related difference in postexercise hypotension underscores the role of a lower orthostatic tolerance in females upon postexercise hemodynamics. The resultant effect is manifested as 1) an attendant elevation in esophageal and muscle tissue temperature in females (182); and 2) an increased postexercise onset threshold for cutaneous vasodilation (40) and sweating (176) relative to males. Moreover, the sweating/skin blood flow to core temperature relationship differs between males and females at greater exercise intensities manifested as a greater latent period for onset of sweating in females as compared to males (182).

The observed differences between males and females do not appear to be influenced by either menstrual cycle phase or oral contraceptive use. Kenny *et al.* (232) reported a similar overall pattern and magnitude of local cutaneous vasodilation and sweating during a thermal challenge performed with or without prior exercise. However, the pre- and postexercise onset thresholds occurred at a higher temperature in the mid-luteal phase as compared to follicular phase. This was not associated with a concomitant change in the postexercise hypotension response. A comparable response was observed with oral contraceptive use with a greater attenuation of the heat loss responses measured during the active pill consumption (high exogenous hormone phase) versus placebo (low exogenous hormone phase). Similarly, no differences in mean arterial pressure response were noted.

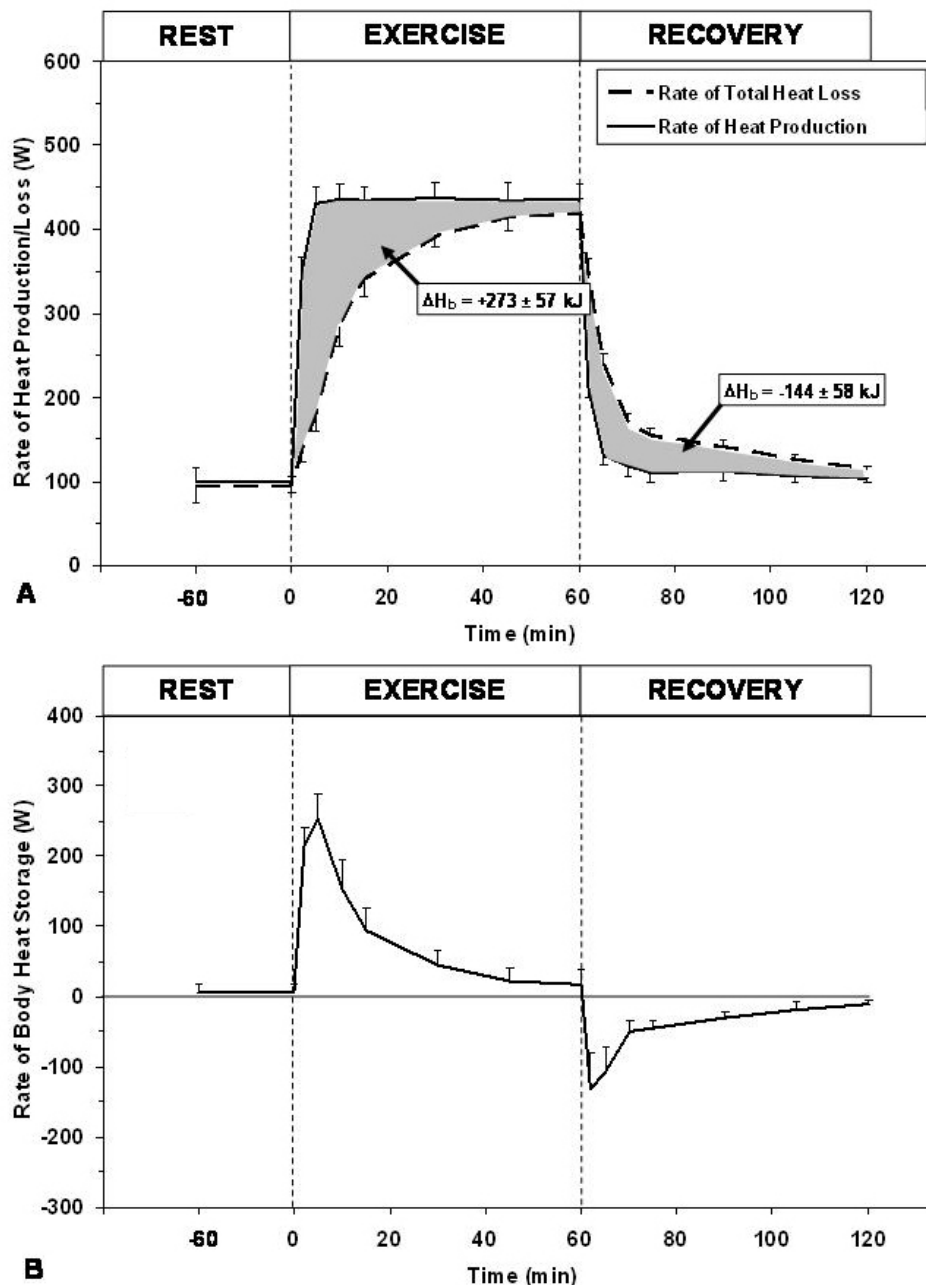
Given the apparent correlation between postexercise cardiovascular regulation and thermal responses, it has been surmised that thermoregulatory responses to postexercise interventions that engage the baroreceptors may differ between males and females. McInnis *et al.* (183) compared the effect of baroreceptors on cutaneous vascular conductance and sweating during the postexercise period in males (183). They showed that the application of 15° head down tilt, which is known to engage baroreceptors, significantly attenuates the reduction in cutaneous vascular conductance, sweat rate and mean arterial pressure typically observed during recovery from exercise in the upright seated position. The augmented heat loss responses observed in the head-down tilt position also resulted in an increased rate of core temperature decay. In a subsequent study, Journeay *et al.* (181) reported that, after accounting for any differences between sexes at preexercise

baseline rest, the application of 15° head-down tilt during postexercise recovery attenuated the fall in mean arterial pressure, cutaneous vascular conductance and sweat rate when compared to the upright seated posture in both males and females. However, the magnitude of change of these thermal and nonthermal responses during the tilt intervention was independent of sex. Further, the augmented cardiovascular and heat loss responses were associated with an increased rate of core temperature decay relative to the upright seated condition in both males and females.

Journeay *et al.* (194) observed that while males and females share the nonthermal mechanoreceptor and baroreceptor influences on cutaneous vascular conductance, they differ in the nonthermal contribution of central command. Whereas, cutaneous vascular conductance can be modulated by central command in females, differences in baroreceptor unloading status and not factors attributed to central command appears to be the main determinant of postexercise cutaneous vascular conductance response in males (177). However, in the presence of greater thermal drive, Gagnon *et al.* (207) reported that attenuating the baroreceptor unloading effect of inactive recovery by activation of the skeletal muscle pump/mechanoreceptors and not central command preserves cutaneous vascular conductance similarly in both hyperthermic males and females.

## 13. HUMAN HEAT BALANCE DURING AND FOLLOWING DYNAMIC EXERCISE: A CALORIMETRIC PERSPECTIVE

The primary evidence for the disturbance in postexercise thermoregulation has been based upon the rapid reduction in local measurements of heat loss responses. Local sweat rate of the forearm (40, 89, 173, 183), forehead (233), upper back (175, 176, 181, 183) and chest (173, 202) using the ventilated capsule techniques have been used to indicate changes in evaporation. Such measurements reflect changes in localized sweating activity only and if these reductions are counter-balanced by increased sweat rate at other sites of the body, postexercise whole-body evaporative heat loss may not be compromised. Similarly, skin blood flow to local areas such as the forearm, chest (173, 174, 186) and thigh (175) have been used to indicate changes in thermal conductivity and it has also been used as an index of dry heat loss postexercise. However, local heat loss responses do not illustrate how much whole-body heat transfer is altered, and core temperature measurements do not accurately represent the magnitude of residual body heat storage (234). It is generally accepted that the only way to accurately estimate the rates of whole-body evaporative and dry heat loss as well as the change in body heat content in humans is by performing simultaneous minute-by-minute measurements of the individual heat balance components by whole-body calorimetry (235). In the following section we will examine the net effect of the postexercise exercise disturbance on thermoregulatory control on whole-body heat loss and body heat storage.



**Figure 8.** Mean whole-body calorimetry data for rate of total heat production (metabolic rate minus rate of external work) and rate of net heat loss (net evaporative and dry heat loss) (Panel A), and the resultant rate of body heat storage (Bottom, Panel B) after 60-min pre-exercise rest, followed by 60-min cycling at 70 W and 60-min of inactive postexercise recovery. Shaded areas represent the positive change in body heat content (+ $\Delta H_b$ ) during the exercise period and the negative change in body heat content (- $\Delta H_b$ ) during the recovery period. Reproduced with permission from, ref 98.

**14. TIME COURSE OF THERMOGENESIS AND THERMOLYSIS DURING AND FOLLOWING STEADY-STATE EXERCISE**

Body heat storage and changes in core temperature are a direct result of a thermal imbalance between the rate of heat production (i.e. metabolic rate minus work rate) and the rate of total heat dissipation to the

surrounding environment (236). For any given steady-state core temperature, a balance between rates of heat production and total heat dissipation (i.e. a rate of body heat storage of zero) must be attained (237). At the onset of exercise, heat production is instantly elevated (Figure 8) due to the liberation of energy supplying the demands of the working muscle groups. During steady-state exercise, the rate of heat production remains constant so long as the

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mechanical efficiency remains unchanged. In contrast, the rate of thermolysis is much slower to respond, with a slight delay after the onset of exercise followed by an exponential increase with a time constant of ~10 minutes (238, 239). The initial mismatch between total heat loss and metabolic heat production will lead to a change in body heat content, with the length of time taken for both rates to match dictating the amount of heat that will be stored in the body. Intense exercise, especially under hot/humid environmental conditions and/or coupled with insulative protective clothing will increase this thermal inertia (134) or temporal dissociation (135) resulting in a greater rate of body heat storage and change in body heat content. The change in body heat content during exercise will be paralleled by a change in core temperature. For core temperature to reach a steady-state value during exercise, an equilibrium between the rates of metabolic heat production and total heat loss (i.e. heat balance) must be achieved (237, 240). Under conditions that favor heat exchange from the body to the environment, the reflex physiological mechanisms that increase the rate of evaporative heat loss (sweating) and the rate of radiative, conductive and convective heat loss (cutaneous vasodilation) combine to elicit an overall thermolytic rate to match the elevated rate of thermogenesis after 50 to 60 minutes of continuous exercise.

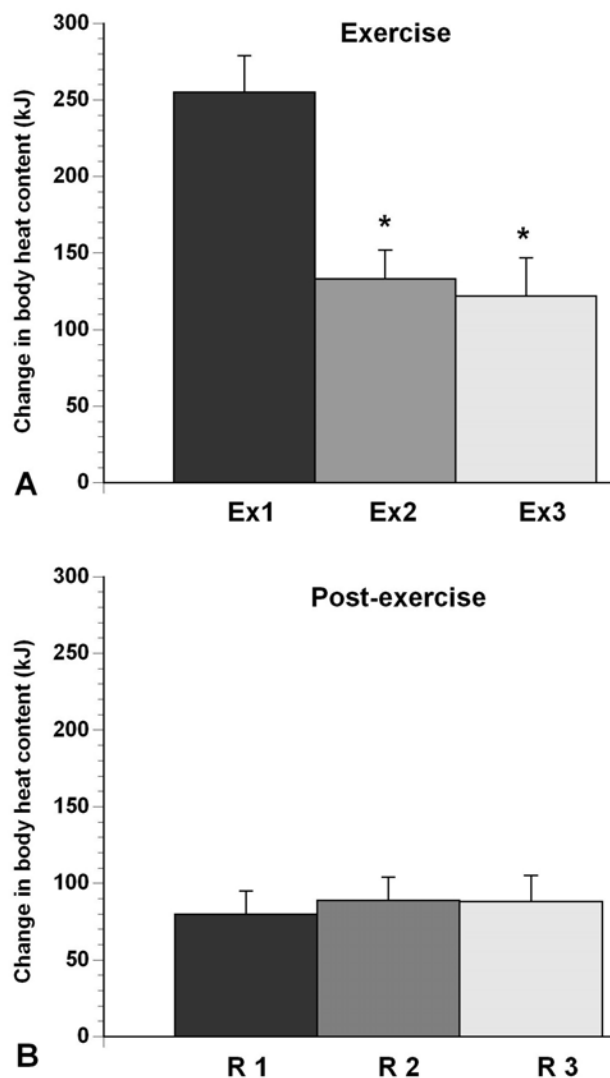
### 15. CALORIMETRIC EVIDENCE FOR NONTHERMAL MODULATION OF WHOLE-BODY HEAT LOSS

As outlined earlier in this review, recovery from dynamic exercise results in significant perturbations of thermoregulatory control. These perturbations evoke a prolonged elevation in core temperature and a concomitant suppression of thermoeffector activity in the early stages of recovery. There is growing empirical evidence indicating that the underlying mechanism for the perturbation of postexercise thermoregulatory control is due to nonthermal baroreflex activity associated with the marked cardiovascular changes that occur after dynamic exercise (174-176, 180, 182, 183, 185). While these studies provide important insight into the etiology of the postexercise disturbance in thermal homeostasis, there remains a paucity of information relating the impact of thermal and nonthermal factors associated with a prolonged hyperthermic state following exercise on whole-body heat balance. While local sweating and skin blood flow responses suggest that the capacity for heat loss in the postexercise recovery period is acutely compromised, the ultimate effect of these changes on whole-body heat loss responses, and therefore body heat storage, are unclear. To date, the magnitude of the change in body heat content during postexercise recovery has only ever been estimated using correlate estimations of core, skin and muscle temperature. While these data may provide an insight into regional tissue heat distribution, such measurements have been recently demonstrated to be a poor indicator of changes in the change in body heat content (234, 241).

In recent work, Kenny and colleagues (98) examined the rates of whole-body evaporative and dry heat loss as well as the change in body heat content during 60

minutes of moderate intensity exercise followed by 60 minutes of postexercise recovery. They postulated that in keeping with previous observations of a rapid reduction in local sweat rate and skin blood flow, a rapid reduction in whole-body evaporative and dry heat loss would occur during postexercise recovery. To quantify whole-body changes in dry and evaporative heat loss, the Snellen whole-body air calorimeter was used. A full technical description of the fundamental principles and performance characteristics of the Snellen calorimeter is available (242). Eight participants cycled for 60 minutes at an external work rate of 70 W (equivalent rate of heat production of ~440 W) followed by 60 minutes of recovery, in a calorimeter at 30°C and 30% relative humidity. A key finding was the observation that only 53% of the heat stored during the exercise bout was dissipated after 60 minutes of recovery in the upright seated posture (Figure 8). At the end of exercise the calculated change in body heat content was +273 kJ whereas the body heat content dissipated during recovery was only 144 kJ. Despite a persistent elevation in core temperature, whole-body evaporative heat loss decreased rapidly in the early stages of recovery which was also accompanied by minimal rates of dry heat loss. These findings are consistent with the numerous reports which demonstrate that muscular work causes an increase in core temperature that persists following exercise. Indeed, in the absence of the heat producing events of exercise, studies show that the elevation in core temperature can persist well beyond 60 minutes of recovery (178, 179). In parallel to the sustained elevation in body heat content (and core temperature), Kenny *et al.* (98) reported sustained elevations in muscle temperature in different regions of the body (i.e., vastus lateralis, triceps brachii and upper trapezius). In particular, a significant elevation of 1.00°C was evident even after 60 minutes of postexercise recovery for the previously active vastus lateralis muscle group. Previous studies have postulated that in conjunction with a rapid reduction in skin perfusion, sweating and whole-body heat loss, and a decrease in circulatory convective heat transfer following the cessation of exercise, a time-dependent transfer of heat from previously active muscle to the central core body region would likely contribute to a prolonged elevation of core temperature (182). This is supported by the findings of Kenny *et al.* (98) which show that under thermoneutral conditions the sustained elevation in core temperature is paralleled by a marked residual heat load at the end of 60 minutes of recovery.

Under high heat stress conditions a greater thermal strain is evident when the volume of work is performed intermittently versus continuously as evidenced by a marked increase in core temperature (243). This response is thought to be related to the overriding nonthermal influence on core temperature regulation associated with the work/rest transitions (219, 243). In support of this hypothesis, it has been shown that intermittent exercise results in a progressive increase in core temperature although the magnitude of increase in the postexercise elevation in core temperature is reduced with successive work/rest intervals (219, 243-247). For example, Kenny *et al.* (219) showed that while the postexercise elevation in core temperature achieved a



**Figure 9.** Change in body heat content during the 30-min exercise for Ex1, Ex2, and Ex3 (top panel, A) and the 15-min recovery (R1, R2, and R3) (bottom panel, B). Final recovery period (R3) extended to 60-min in duration. Asterisk (\*), indicates values significantly different from Ex1. Error bars indicated standard deviations. Reproduced with permission from, ref 104.

higher absolute temperature with successive exercise bouts, the magnitude of increase was less in the subsequent exercise/recovery cycles (i.e., 0.48°C, 0.15°C and 0.11°C for the first, second and third 15 minutes exercise/30 minutes recovery cycle respectively). Despite a progressively greater thermal drive, the decline in the rate of local heat loss during successive recovery bouts was the same. Taken together, these findings suggest the possibility that the greater thermal strain observed during intermittent exercise may in part be the result of a nonthermal mediated attenuation of the rate of local heat loss responses during exercise.

To evaluate this hypothesis, Kenny *et al.* (104) studied heat balance during thermal transients caused by successive exercise bouts. Ten participants performed three successive 30 minute bouts of cycling at a constant rate of heat production of ~500W, each separated by 15

minute rest under thermoneutral ambient conditions. In keeping with previous reports, they showed that the additional amount of heat stored in the body subsequent to the first (256 kJ) exercise/rest cycle was significantly less during the second (135 kJ) and third (124 kJ) exercise/rest cycles (Figure 9). The difference in the amount of heat stored with the successive exercise bouts was associated with a more rapid increase in whole-body heat loss observed with each successive exercise bout and not due to an increase in the rate of whole-body heat loss in recovery. Similar changes in body heat content (-82 kJ, -91 kJ and -88 kJ for the first, second and third recovery periods respectively) were measured during each of the successive 15 minute recovery periods. The greater rate of increase in whole-body heat loss observed in the second and third exercise bouts suggests that the thermal inertia is reduced when the body is already warm and much of the heat already stored during the first exercise/recovery cycle

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remains. However, their findings suggest that nonthermal factors may predominate during the subsequent exercise bouts as evidenced by the similarity in whole-body heat loss in the two successive exercise bouts despite a cumulative increase in body heat content. Indeed, despite cumulative residual heat storage and elevated core and muscle tissue temperatures, whole-body evaporative heat loss decreased rapidly in the early stages of recovery which was also accompanied by minimal dry heat loss. From a mechanistic point of view, the postexercise reduction in heat loss responses demonstrates that nonthermal stimuli maintain a strong overriding influence on thermoeffector activity even in the presence of the progressively greater thermal drive associated with intermittent exercise.

As described earlier in this review, in addition to thermal controllers of thermoeffector activity (102, 137), many nonthermal factors such as baroreceptors, metaboreceptors, mechanoreceptors/muscle pump and central command (177, 194) can impinge on the thermoregulatory system thereby altering thermoeffector response. It is possible that in parallel to the greater thermal drive associated with intermittent exercise (219) the relative influence of different nonthermal inputs on core temperature regulation may vary (207). Some insight relating the interaction of thermal and nonthermal stimuli on thermoregulatory control can be gleaned from more recent studies examining heat balance using recovery mode as a variable to control for nonthermal afferent activity. Evidence for nonthermal factors upon postexercise thermoregulation have been typically sought by comparing the absolute values of heat loss responses between recovery conditions. Jay *et al.* (205) observed that despite a smaller postexercise reduction in the rates of heat production and heat loss, the changes in body heat content at the end of a 30 minute recovery measured using calorimetry were similar between active and inactive recoveries. This was paralleled by a similar core temperature response. From a heat balance perspective, if the rate of decrease of whole-body heat loss had been proportional to the magnitude of decrease in heat production, the residual heat storage would have been greater (and core temperature higher) in the active relative to inactive recovery. However, it was shown that relative to the magnitude of decrease in the rate of metabolic heat production, the rate of decay of whole-body heat loss was significantly less for active recovery relative to inactive recovery. The correspondingly slower rate of decay observed in response to the higher rate of metabolic heat production of the active recovery provides additional evidence in support of nonthermal modulation of postexercise thermoeffector activity.

Active (loadless pedaling) and passive (assisted pedaling) recoveries have been shown to reverse the postexercise suppression of local heat loss responses following a single bout of dynamic exercise. However, it remained unclear if this postexercise maintenance of heat loss would result in a smaller cumulative change in body heat content. A recent study conducted in our laboratory examined the effect of active, passive, and inactive recovery on heat balance during three 15 minute bouts of

moderate intensity exercise (150 W) separated by three 15 minute recoveries during which participants either 1) performed loadless pedaling at 40 rpm (active recovery); 2) remained upright seated while the lower limbs were passively compressed (passive recovery); or 3) remained resting in an upright seated posture (inactive recovery). During active recovery, the rate of heat production was greater by ~50 W at the end of each recovery period compared to both the passive and inactive modes. This was paralleled by a greater rate of whole-body heat loss compared to inactive recovery at the end of the first (246 W vs. 188 W), second (264 W vs. 209 W), and third (248 W vs. 208 W) recoveries respectively. In contrast, whole-body heat loss was similar between active and passive recoveries. These findings show that passive recovery, which provides a rate of metabolic heat production comparable to inactive recovery but a higher rate of whole-body heat loss similar to an active recovery, results in a lower cumulative change in body heat content as measured at the end of three exercise/recovery cycles (i.e., passive: 351 kJ, active: 367 kJ and inactive: 412 kJ).

## 16. SUMMARY

It is evident that the actions of nonthermal factors have important consequences in the regulation of body core temperature during and following exercise. While the action of these nonthermal factors is largely considered to be an inhibitory or excitatory stimulus which displaces the set-point about which temperature is regulated, their effects on human thermoregulatory control are far reaching. This is best evidenced by the postexercise disturbance in thermal homeostasis. Despite our increasing knowledge of thermal and nonthermal mechanisms governing temperature regulation, more research is needed to understand how these factors contribute to whole-body human homeothermy.

## 17. ACKNOWLEDGEMENTS

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