

## Skin Blood Flow in Adult Human Thermoregulation: How It Works, When It Does Not, and Why

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The thermoregulatory control of human skin blood flow is vital to the maintenance of normal body temperatures during challenges to thermal homeostasis. Sympathetic neural control of skin blood flow includes the noradrenergic vasoconstrictor system and a sympathetic active vasodilator system, the latter of which is responsible for 80% to 90% of the substantial cutaneous vasodilation that occurs with whole body heat stress. With body heating, the magnitude of skin vasodilation is striking: skin blood flow can reach 6 to 8 L/min during hyperthermia. Cutaneous sympathetic vasoconstrictor and vasodilator systems also participate in baroreflex control of blood pressure; this is particularly important during heat stress, when such a large percentage of cardiac output is directed to the skin. Local thermal control of cutaneous blood vessels also contributes importantly—local warming of the skin can cause maximal vasodilation in healthy humans and includes roles for both local sensory nerves and nitric oxide. Local cooling of the skin can decrease skin blood flow to minimal

levels. During menopause, changes in reproductive hormone levels substantially alter thermoregulatory control of skin blood flow. This altered control might contribute to the occurrence of hot flashes. In type 2 diabetes mellitus, the ability of skin blood vessels to dilate is impaired. This impaired vasodilation likely contributes to the increased risk of heat illness in this patient population during exposure to elevated ambient temperatures. Raynaud phenomenon and erythromelalgia represent cutaneous microvascular disorders whose pathophysiology appears to relate to disorders of local and/or reflex thermoregulatory control of the skin circulation.

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AVA = arteriovenous anastomoses; CGRP = calcitonin gene-related peptide; DM = diabetes mellitus; ERT = estrogen replacement therapy; L-NAME = N<sup>G</sup>-nitro-L-arginine methyl ester; NPY = neuropeptide Y; PO/AH = preoptic/anterior hypothalamus

Skin blood flow in humans can increase substantially in response to thermal stress: thermoregulatory vasodilation can increase skin blood flow to 6 to 8 L/min during severe hyperthermia.<sup>1-3</sup> Such responses in the skin circulation represent a vital aspect of normal thermoregulation in humans. Vasodilation and increased skin blood flow (in concert with sweating) are essential to heat dissipation during heat exposure and exercise. During cold exposure, vasoconstriction in the skin decreases heat loss from the body and protects against hypothermia. Therefore, altered control of skin blood flow has important clinical implications and can substantially impair the ability to maintain normal body temperatures. With menopause, thermoregulatory control of skin blood flow is altered by changes in reproductive hormone levels.<sup>4,5</sup> This may contribute to the occurrence of hot flashes, but the mechanisms responsible are poorly understood. In patients with type 2 diabetes mellitus (DM), im-

pairments in cutaneous vascular control might contribute to the increased incidence of heat illness (heat stroke, heat exhaustion) during elevated ambient temperatures.<sup>6,7</sup>

Despite these important implications, several misconceptions persist in the current literature. For example, it is commonly (and incorrectly) believed that sympathetic neural control of skin blood flow in humans includes only vasoconstrictor nerves, that cutaneous neurovascular control is not regulated by blood pressure-regulating autonomic reflexes (baroreflexes), and that local release of bradykinin is responsible for cutaneous vasodilation during whole body heating. This review focuses on current concepts regarding mechanisms of thermoregulatory control of human skin blood flow and how changes in these mechanisms can contribute to thermoregulatory dysfunction in menopause, type 2 DM, and cutaneous microvascular disorders.

### SKIN BLOOD FLOW AND THERMOREGULATION IN HUMANS

#### Overview of the Role of the Skin in Human Physiological Thermoregulation

Physiological thermoregulation in humans comprises changes in heat dissipation (cutaneous vasodilation and sweating) and heat generation (shivering) in response to various internal and external thermal stimuli. The central control of thermoregulation is in the preoptic/anterior

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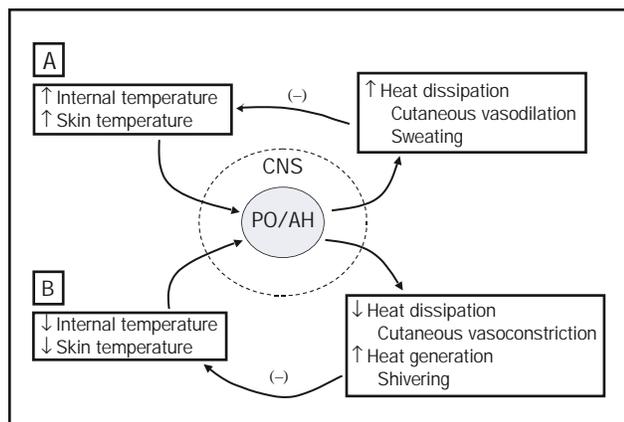


Figure 1. Negative feedback loops involved in physiologic thermoregulation in humans. Minus signs refer to the correction of the error signal (change in skin and/or internal temperature) by the appropriate effector response. A, Increases in internal and/or skin temperatures are sensed by the preoptic/anterior hypothalamus (PO/AH) and result in increased heat dissipation via cutaneous vasodilation and sweating, which then corrects the original increased temperature. The influence of internal temperature is several times that of skin temperature in the control of these effectors. B, Decreased skin or internal temperature causes reflex decreases in heat dissipation (cutaneous vasoconstriction) and increased heat generation (shivering) to correct the decreases in temperature that initiated those changes. CNS = central nervous system.

hypothalamus (PO/AH) in the brain. Information on internal (core) and surface (skin) temperatures is relayed to the PO/AH, which then coordinates the appropriate efferent response.<sup>8,9</sup> Conceptually, this area of the brain can be related to a thermostat, which initiates heat dissipation responses when body temperature is sensed as “too hot” and heat conservation or heat generation when temperature is sensed as “too cold.” Control of thermoregulation by the PO/AH is summarized in Figure 1. Human thermoregulation has been comprehensively reviewed in several books<sup>10,11</sup> and recent review articles.<sup>12-15</sup>

Resting skin blood flow in thermoneutral environments is approximately 250 mL/min, which results in a heat dissipation of approximately 80 to 90 kcal/h, about the level of resting metabolic heat production.<sup>1,16</sup> During exercise or heat exposure, increases in body temperature trigger cutaneous vasodilation and sweating.<sup>1,17</sup> Cutaneous vasodilation increases blood flow to the skin severalfold, substantially increasing convective transfer of heat from the core to the periphery. These large increases often require increased cardiac output and redistribution of blood flow from areas, such as the splanchnic region, that demonstrate vasoconstriction. These adjustments are usually sufficient to match the demand for increased skin blood flow, such that oxygen supply to organs such as the heart is not compromised.<sup>1</sup>

Concurrent with cutaneous vasodilation, the evaporation of sweat decreases skin temperature, thereby cooling the blood in the dilated skin vessels before it returns to the core. In general, skin blood flow and sweating continue to increase in proportion to internal temperature until a steady state is reached at which heat dissipation and heat generation are equal, and therefore body temperature is constant, or until maximal responsiveness is reached. When internal temperature decreases toward normal, sweating stops, and skin blood flow returns to normal. In this sense, thermoregulation represents a classic negative feedback loop (Figure 1, A).

During whole body heating, there are identifiable internal temperature thresholds for cutaneous vasodilation and sweating.<sup>1,17</sup> These are defined as the internal temperatures at which cutaneous vasodilation or sweating begins (Figure 2). Furthermore, the gain or sensitivity of the sweating or vasodilator response with respect to internal temperature can be identified as the slope of the skin blood flow–internal temperature relationship after threshold. These 2 functional parameters provide insight into mechanisms of an altered response. For example, lower skin blood flow at a given internal temperature during heat stress could be due to an increased threshold for vasodilation (such that vasodilation does not begin until a higher internal temperature is reached), a decrease in the sensitivity of the response, or some combination of both.

A schematic example of 2 cutaneous vasodilator responses as functions of internal temperature during body heating is shown in Figure 2. These responses have different thresholds but similar sensitivities, resulting in substantial differences between responses in the level of skin blood flow (and thus heat dissipation) for a given level of internal temperature. Examples of factors that can alter the threshold and/or sensitivity of cutaneous vasodilation are heat acclimation,<sup>18</sup> exercise training,<sup>18</sup> circadian rhythm,<sup>19,20</sup> and, in women, reproductive hormone status.<sup>4,5,21,22</sup>

On exposure to cold environments, skin blood flow decreases via cutaneous vasoconstriction. This results in a decrease in heat dissipation from the skin surface and less convective heat transfer from the core to the surface. With further body cooling, shivering begins. The muscular contractions involved result in increased heat generation, which in combination with decreased heat dissipation helps to maintain core temperature in the face of cold exposure.

Measurement of skin blood flow is usually accomplished by laser Doppler flowmetry or venous occlusion plethysmography.<sup>1,23,24</sup> Laser Doppler measurement of skin blood flow is based on the Doppler shift of incident laser light when it is reflected off moving red blood cells.<sup>24</sup> This method offers the advantages of high temporal resolution (measurements can be taken continuously) and specificity to the cutaneous microcirculation.<sup>24,25</sup> The disadvantages of

this method include the inability to measure absolute flow values (ie, flow is measured in arbitrary laser Doppler units or volts rather than in milliliters per minute) and the restriction to a relatively small area of measurement. The former disadvantage is often overcome by normalizing laser Doppler flowmetry values to values measured during maximal vasodilation (with either local warming of the skin or local sodium nitroprusside).<sup>21,26,27</sup> Venous occlusion plethysmography can be used to measure blood flow in the forearm, lower leg, or finger. In the forearm or the lower leg, it can be used to measure changes in skin blood flow in situations in which blood flow to underlying muscle does not change (ie, passive heat stress). In the finger, the contribution of muscle blood flow is much lower; however, this measurement includes areas of both glabrous skin (palmar side) and nonglabrous skin (dorsal aspect),<sup>28</sup> which can limit data interpretation, depending on the issues being addressed. Venous occlusion plethysmography can be used to measure absolute changes in skin blood flow (eg, with body heating) but has the disadvantages of not being specific to the skin (if muscle blood flow changes, data can be difficult to interpret) and providing discontinuous measurements (usually at most 4 measurements per minute).

### Reflex Neural Control of Skin Blood Flow via Sympathetic Vasoconstrictor and Vasodilator Nerves

The human cutaneous circulation is unique in that it is controlled by 2 populations of sympathetic nerves. The well-known sympathetic adrenergic vasoconstrictor nerves coexist with sympathetic vasodilator nerves, a less well-understood system that is activated during hyperthermia. Sympathetic vasoconstrictor and vasodilator nerves innervate all areas of nonglabrous skin, whereas areas of glabrous skin (palms, soles, lips) are innervated only by sympathetic vasoconstrictor nerves.<sup>1</sup> Another important distinction between glabrous and nonglabrous skin is the existence of arteriovenous anastomoses (AVA), which are thick-walled, low-resistance conduits that allow high flow rates directly from arterioles to venules. In glabrous skin, AVA are numerous and richly innervated by sympathetic vasoconstrictor nerves. Therefore, in these areas, opening or closing of these AVA can cause substantial changes in skin blood flow.<sup>29</sup> In contrast, nonglabrous skin has few if any AVA and is innervated by both sympathetic vasoconstrictor and vasodilator nerves.<sup>1,16</sup>

Sympathetic vasoconstrictor nerves release norepinephrine, which interacts with postsynaptic  $\alpha_1$ - and  $\alpha_2$ -receptors on cutaneous arterioles and AVA. In addition, noradrenergic vasoconstrictor nerves release one or more cotransmitters that also cause vasoconstriction.<sup>30,31</sup> Although animal models suggest roles for neuropeptide Y (NPY) and/or adenosine triphosphate as adrenergic cotransmitters mediating cutane-

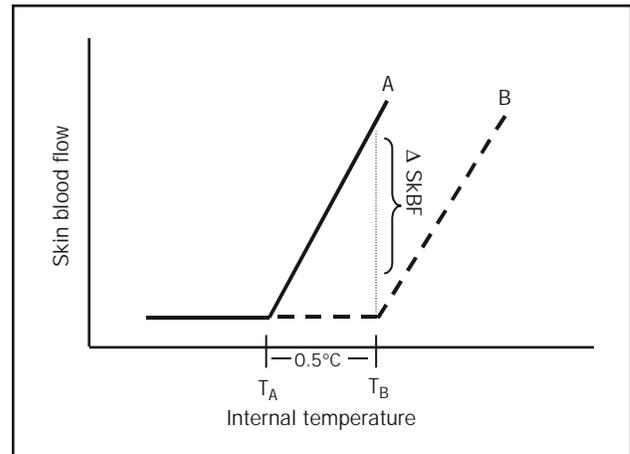


Figure 2. Schematic examples of skin blood flow responses during whole body heating.  $T_A$  and  $T_B$  represent internal temperature thresholds,  $0.5^\circ\text{C}$  apart, for responses A and B, respectively. The slope of each line after threshold represents the sensitivity of the vasodilator response. The vertical line is included to emphasize the large differences in skin blood flow at a given internal temperature with this apparently small difference in threshold.  $\Delta \text{SkBF}$  = change in skin blood flow.

ous vasoconstriction,<sup>32,33</sup> the identity of those that participate in human reflex vasoconstriction remains to be elucidated.

The vasoconstrictor system in human skin is tonically active in thermoneutral environments.<sup>34</sup> Therefore, subtle changes in the activity of this system during most daily activities are responsible for maintenance of normal body temperature with slight changes in activity or ambient temperature. This is possible because small changes in skin blood flow can cause relatively large changes in heat dissipation. For example, a change in skin blood flow from resting neutral levels of as little as 8 mL per 100 mL/min over the entire body surface results in a doubling of heat transfer to the environment.<sup>16</sup> This allows for a zone of thermoregulation (referred to as the “neutral” or “vasomotor” zone) that is accomplished solely via changes in cutaneous vasomotor tone.<sup>35</sup> The vasoconstrictor system is also responsible for the decreases in skin blood flow that occur with cold exposure. Withdrawal of the activity of these nerves is responsible for 10% to 20% of the cutaneous vasodilation during hyperthermia.<sup>1,34</sup>

With hyperthermia in humans, skin blood flow can increase to as much as 6 to 8 L/min or 60% of cardiac output.<sup>32</sup> The large increases in skin blood flow are mediated primarily (80%-90%) by activation of sympathetic vasodilator nerves in the skin.<sup>1,3</sup> The sympathetic active vasodilator system in humans is not tonically active in normothermia and is only activated during increases in internal temperature, such as those that occur during exercise or environmental heat exposure.<sup>1,36,37</sup>

The existence of sympathetic active vasodilation in human skin has been recognized since the 1930s.<sup>38,39</sup> The original observations were based on measurement of skin temperature and visual observation of flushing in normal and sympathectomized limbs during passive body heating. In the 1950s, Edholm et al<sup>40,41</sup> and Roddie et al<sup>42</sup> showed that the increase in skin blood flow with body heating was blocked by anesthetic blockade of cutaneous nerves. Roddie et al<sup>42</sup> further showed that nerve block during heating decreased skin blood flow to preheating levels. Studies<sup>40,43</sup> from that era also showed that skeletal muscle blood flow does not increase during resting heat stress, such that all increases in limb blood flow during passive heating are due to increased skin blood flow.

Current evidence suggests that active vasodilation is mediated by cotransmission from sympathetic cholinergic nerves. Local presynaptic inhibition of cholinergic nerves with botulinum toxin abolishes active cutaneous vasodilation.<sup>44</sup> Since postsynaptic muscarinic inhibition with atropine does not block this vasodilation, it is unlikely that acetylcholine is responsible.<sup>44-46</sup> However, the cotransmitter itself has not been identified.

Earlier studies<sup>47,48</sup> regarding the mechanism of active cutaneous vasodilation suggested that bradykinin was the vasodilator substance responsible, secondary to sweat gland activity, such that the active vasodilator process was mediated indirectly via sudomotor nerves. However, although sweating and cutaneous vasodilation are functionally linked and often temporally coincident, changes in one system do not always parallel changes in the other. For example, short-term exercise increases the internal temperature threshold for cutaneous vasodilation (compared with resting heat stress) but does not affect the threshold for sweating.<sup>49,50</sup> Furthermore, a recent study<sup>51</sup> showed no change in active cutaneous vasodilation with blockade of bradykinin B2 receptors, although the inhibitor effectively blocked all vasodilation to exogenous bradykinin. Thus, bradykinin does not appear to mediate active cutaneous vasodilation. The exact nature of the relationship between sudomotor and active vasodilator nerves, as well as the vasodilator substance itself, remains to be elucidated.

The mechanism of active cutaneous vasodilation includes a moderate role for nitric oxide. Recent investigations<sup>26,46</sup> used local cutaneous microdialysis of N<sup>G</sup>-nitro-L-arginine methyl ester (L-NAME) either before or during whole body heat stress to test whether local pharmacologic blockade of nitric oxide synthesis would inhibit active vasodilation. On average, nitric oxide was found to contribute approximately 30% to the active vasodilator response to whole body heat stress.<sup>26,46</sup>

Mechanistically, changes in a skin blood flow response can be due to changes in either the sympathetic vasoconstrictor system or the active vasodilator system. For ex-

ample, a higher threshold for vasodilation during body heating could be due to increased peripheral vasoconstrictor activity, inhibited activity of the vasodilator system, or some combination of both. These 2 mechanisms can be studied separately by using local application of bretylium, a substance that is taken up presynaptically into noradrenergic nerve terminals, where it prevents all neurotransmitter release.<sup>36,52</sup> We<sup>21</sup> and others<sup>4</sup> have used this approach to show that shifts in reflex control of cutaneous vasodilation with female reproductive hormones are due to shifts in control of the active vasodilator system.

### Skin Blood Flow and Blood Pressure Regulation in Normothermia and Hyperthermia

It was previously believed that the baroreflex controls skeletal muscle, but not skin, blood flow. Indeed, muscle sympathetic nerve activity changes in response to baroreflex stimulation, and skin sympathetic nerve activity does not.<sup>53</sup> However, whereas muscle sympathetic nerve activity comprises only vasoconstrictor nerves, skin sympathetic nerve activity includes vasoconstrictor, vasodilator, sudomotor, and piloerector nerves.<sup>1,3</sup> Therefore, it is difficult to interpret a lack of change in skin sympathetic nerve activity with respect to any one of these nerve types.

In fact, both sympathetic vasoconstrictor and vasodilator systems in the skin participate in blood pressure regulation via the baroreflex.<sup>54-58</sup> For example, the skin vasoconstricts in response to "unloading" of the baroreflex using lower-body negative pressure.<sup>54,56,58</sup> In normothermia, this vasoconstriction is caused by an increased activity of the sympathetic vasoconstrictor system and therefore is blocked by local bretylium.<sup>54,56</sup> Since skin blood flow is relatively low in normothermia, this vasoconstriction in the skin is not substantial. In hyperthermia, however, the sympathetic active vasodilator system has been activated, and skin blood flow can reach high levels. When lower-body negative pressure is imposed during hyperthermia, the skin vasoconstricts substantially via withdrawal of vasodilator system activity.<sup>54,56</sup> In hyperthermia, baroreflex-mediated cutaneous vasoconstriction is particularly important with regard to blood pressure regulation since such a large percentage of cardiac output (up to 60%) is directed to the skin for heat dissipation.<sup>1,3</sup> Because of the important roles of the cutaneous sympathetic vasodilator and vasoconstrictor systems in thermoregulation and blood pressure regulation, dysfunction in one or both of these systems could have important consequences for both processes.

### LOCAL THERMAL CONTROL OF SKIN BLOOD FLOW Local Warming of the Skin

In addition to reflex control of skin blood flow by sympathetic vasodilator and vasoconstrictor systems, the local

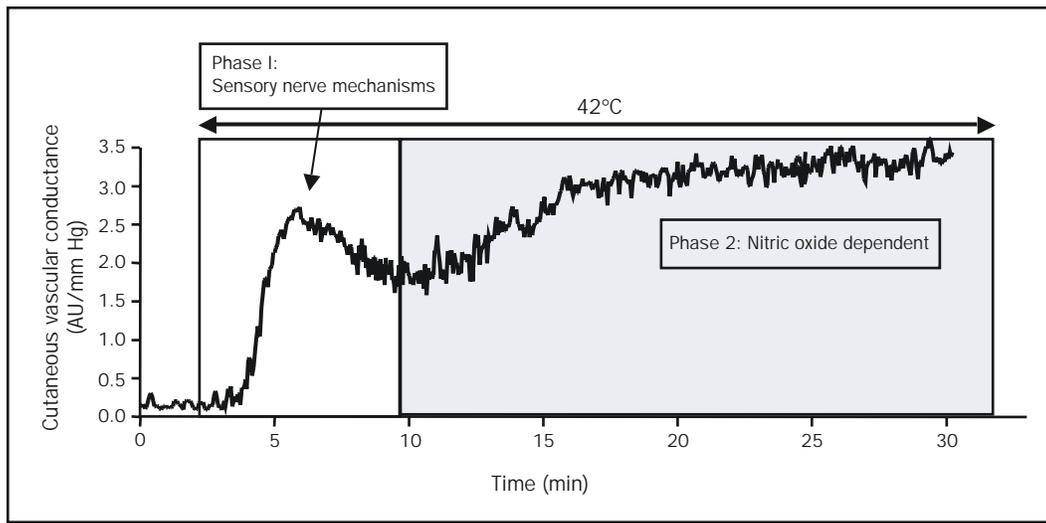


Figure 3. Typical cutaneous vasodilation during 30 minutes of local warming. The initial rapid peak is due to local sensory nerve activity, whereas the second slower phase depends on nitric oxide.

temperature of an area of skin also contributes importantly to the control of skin blood flow at that site. Local warming of the skin causes a direct and substantial vasodilation in the area being warmed. In healthy humans, a sustained local temperature of 42°C causes maximal dilation of skin blood vessels.<sup>59-61</sup> The vasodilator response to this local warming stimulus is biphasic. A typical response to 30 minutes of 42°C local temperature is shown in Figure 3. There is an initial rapid increase in blood flow during the first 3 to 5 minutes, then a moderate decrease, and then a slower vasodilation that attains a plateau after 25 to 30 minutes of warming.<sup>59,62,63</sup> The final level of vasodilation is proportional to the temperature used.<sup>59</sup>

The initial rapid-phase vasodilation during local warming to 42°C relies predominantly on local activity of sensory nerves. Only local neural mechanisms are involved since topical application of a local anesthetic<sup>63</sup> but not proximal neural blockade<sup>59</sup> inhibits this initial peak. The sensory nerves responsible for the local response to heat are primarily C-fiber afferents that, when stimulated, cause localized vasodilation via antidromic release of calcitonin gene-related peptide (CGRP), substance P, and neurokinin A.<sup>64</sup> These afferents are stimulated by capsaicin, the pungent ingredient in hot peppers. Capsaicin binds to vanilloid receptors (VR1) on nerve endings and causes depolarization via opening of a cation channel. This results in a local sensation of heat and vasodilation. VR1 is also directly activated by heat and low pH.<sup>65</sup> Recently, a new member of the vanilloid receptor family (VRL3 or TRPV3) has been identified and localized to the skin.<sup>66,67</sup> Thus far, TRPV3 has been localized predominantly in keratinocytes of the epidermis (outermost layer of skin).<sup>68,69</sup> Interestingly, this

receptor is temperature sensitive (activated at temperatures at or above 39°C) but capsaicin insensitive and probably contributes to activation of cutaneous heat-sensitive afferents at higher local temperatures along with VR1.<sup>66-68</sup>

To investigate the role of these heat-sensitive afferents at lower levels of local temperature, we<sup>70</sup> measured skin vasodilation at local temperatures between 20°C and 42°C in combination with local capsaicin treatment to chemically stimulate heat-sensitive sensory nerves. Using various combinations of chemical (capsaicin) and thermal stimulation of small areas of skin, we showed that activation of these nerves contributes to local warming vasodilation at temperatures ranging from 29°C to 40°C.<sup>70</sup>

Although blockade of local neural activity inhibits the initial, rapid vasodilation to local warming, it has no effect on the second, slower phase of the response. Nitric oxide has an important role in both the initiation and the maintenance of this phase. Local L-NAME (a nitric oxide synthase inhibitor) inhibits this vasodilation when administered either before local heating or after vasodilation has reached a plateau.<sup>60,63</sup>

### Local Cooling of the Skin

Local cooling of the skin produces a powerful localized vasoconstriction that can decrease skin blood flow essentially to zero. This vasoconstriction depends on local activation of adrenergic nerves and is reversed by local noradrenergic inhibition with bretylium.<sup>59</sup> An increase in the affinity of postsynaptic  $\alpha$ -receptors (especially  $\alpha_2$ -receptors) with decreasing temperature also contributes to this local vasoconstriction.<sup>71,72</sup> This response does not require

intact connection to the central nervous system because it is not affected by proximal neural blockade.<sup>59</sup>

### SKIN BLOOD FLOW AND FEMALE REPRODUCTIVE HORMONES: IMPLICATIONS FOR MENOPAUSE

Menopausal hot flashes are a well-recognized but poorly understood dysfunction of the human thermoregulatory system. Although estrogen deficiency clearly contributes to this phenomenon, the mechanisms involved are unknown. Some insight into this issue comes from studies of the influences of female reproductive hormones on control mechanisms of skin blood flow.<sup>15</sup> Both estrogen and progesterone appear to influence skin blood flow control in both young women<sup>15,21,73</sup> and postmenopausal women.<sup>4,5</sup> In general, estrogens promote cutaneous vasodilation and therefore heat dissipation. The effect of progesterone is less clear, but this hormone is considered "thermogenic," possibly because it inhibits cutaneous vasodilation.<sup>15</sup>

#### Body Temperature and the Vasoconstrictor System

In postmenopausal women, estrogen replacement therapy (ERT) decreases resting body temperature by approximately 0.5°C.<sup>4</sup> Reproductive hormones also affect body temperature in younger women: it is well known that resting body temperature changes during the menstrual cycle, with an average 0.3°C to 0.5°C increase in the midluteal phase of the menstrual cycle (when progesterone and estrogen levels are elevated) compared with the early follicular phase (when both hormone levels are low). These changes also occur in women taking oral contraceptives.<sup>21,27</sup> Since estrogen alone decreases body temperature in young women as in older women,<sup>4,74</sup> the menstrual cycle-related changes are thought to be primarily effects of progesterone. These hormone-mediated changes in resting body temperature likely include changes in the activity of the vasoconstrictor system. However, the amount with which resting vasoconstrictor system activity would change (based on the changes in body temperature) would be less than 2%<sup>15,35</sup> and is therefore below the resolution of available measurement techniques.

To elucidate any effects of female hormones on vasoconstrictor system function, we<sup>22</sup> recently investigated the control of the cutaneous vasoconstrictor system over a range of skin temperatures in 2 phases of oral contraceptive use. We found that high hormone (estrogen and progesterone) status did not affect the sensitivity of vasoconstrictor responsiveness with respect to skin temperature but did shift the control of the system to higher internal temperatures. Additional studies further showed that reproductive hormone status alters the release of a vasoconstricting neurotransmitter other than norepinephrine.<sup>30</sup> This cotrans-

mitter (possibly NPY) contributes to a greater extent to reflex cutaneous vasoconstriction when progesterone and estrogen levels are elevated compared with when they are low.<sup>30</sup> The influence of estrogen alone on vasoconstrictor system function remains unclear, but its influence in promoting lower body temperature suggests that it inhibits the activity of this system.<sup>4,15</sup>

#### The Active Vasodilator System

Hormone replacement significantly affects the control of cutaneous vasodilation after menopause. In postmenopausal women, ERT decreases the threshold for the onset of cutaneous vasodilation by approximately 0.5°C.<sup>4,5</sup> This apparently small threshold shift results in large increases in skin blood flow for any given level of core temperature during heating (Figure 2). When progesterone was included in the hormone replacement therapeutic regimen, the threshold was shifted back upward such that it did not differ from that in control subjects who were not undergoing hormone replacement therapy.<sup>4,5</sup> The shift in control of the active vasodilator system with estrogen in postmenopausal women is due to a downward shift in the threshold for the onset of active vasodilation.<sup>4</sup> Taken together, these data suggest that estrogen promotes active vasodilator function, whereas progesterone inhibits active vasodilation.

Although changing estrogen levels are implicated in the occurrence of hot flashes during the perimenopausal period, the thermoregulatory mechanisms of this phenomenon are poorly understood. These effects of estrogen on reflex vasodilation in the skin probably contribute. Effects of altered estrogen levels on the central control of thermoregulation (ie, PO/AH neurons)<sup>75</sup> could also contribute to the thermal sensations of hot flashes. Studies of specific mechanisms of skin blood flow control during hot flashes are thus far lacking, and this important topic deserves further attention.

Reproductive hormone status also alters the threshold for cutaneous vasodilation in premenopausal women. In young women taking oral contraceptives, progesterone and estrogen in oral contraceptives cause an increase in the threshold for cutaneous vasodilation (compared with the low hormone phase of the cycle).<sup>21,27</sup> This is also true for the endogenous progesterone and estrogen of the regular menstrual cycle.<sup>19</sup> We<sup>21</sup> showed that in young women, as in postmenopausal women, the shift in threshold with reproductive hormones is due to a shift in the threshold for active vasodilation.

#### Local Temperature Responses

In postmenopausal women, neither resting skin blood flow nor maximal vasodilation to local warming (42°C) is altered by hormone replacement therapy.<sup>76</sup> We found that submaximal local vasodilation to temperatures between

38°C and 42°C was augmented with high hormone status (estrogen and progesterone) in premenopausal women.<sup>73</sup> Since estrogen augments nitric oxide–dependent vasodilation,<sup>77</sup> these results are consistent with previous demonstrations that local warming vasodilation is nitric oxide dependent.<sup>60,63</sup> We found no effect of hormone status on vasoconstrictor responsiveness to local cooling of the skin.<sup>73</sup>

### SKIN BLOOD FLOW AND TYPE 2 DM

Individuals with type 2 DM appear to be at increased risk for heat illness during exposure to elevated ambient temperatures. There was a markedly increased incidence of heat illness (heat stroke, heat exhaustion) in diabetic patients compared with nondiabetic patients during heat waves in New York, NY, and Chicago, Ill.<sup>6,7</sup> This finding may be linked to cutaneous vasodilator dysfunction and suggests a serious impairment in the ability of these patients to thermoregulate in the heat.

There is evidence that local cutaneous microvascular responsiveness is impaired in type 2 DM. Cutaneous vasodilation to local iontophoresis of acetylcholine and sodium nitroprusside (measured by laser Doppler flowmetry) was diminished in DM patients with<sup>78,79</sup> or without<sup>80</sup> neuropathy. Patients with type 2 DM appear to have decreased cutaneous vasodilation to local temperature of 44°C.<sup>78,79</sup> Because this temperature often elicits pain,<sup>81</sup> the relationship between the existence of an altered response and the presence or absence of neuropathy remains to be elucidated. Data from recent preliminary studies in our laboratory suggest that patients with asymptomatic type 2 DM exhibit less vasodilation to nonpainful local warming (42°C) compared with age-matched controls, including significant decreases in both the initial peak and plateau phases of the response (N.C., A. Basu, MD, unpublished data, 2002).

Indirect evidence for impairments in reflex thermoregulatory control of skin blood flow in patients with type 2 DM comes from a large number of studies that show impaired sympathetic neural control of sweating and blood pressure in these patients.<sup>82-85</sup> Because of the functional relationship between the sympathetic vasodilator and sudomotor systems, it is likely that sympathetic vasodilator neural function in the skin is also impaired in patients with type 2 DM. Taken together with the known impairments in local vasodilator function in type 2 DM, these data suggest impaired thermoregulatory control of skin blood flow in these patients. This is an important area for future research.

### CUTANEOUS MICROVASCULAR DISORDERS

Two important cutaneous microvascular disorders that may be related to altered reflex or local thermoregulation are Raynaud phenomenon and erythromelalgia. Neither disorder

is well understood with regard to etiology or pathophysiology.

Raynaud phenomenon affects 3% to 5% of the general population and is characterized by hyperreactive vasoconstriction of the periphery, most often fingers and toes, which can result in pronounced ischemia-reperfusion injury to the skin. Patients with this disorder exhibit excessive vasoconstriction in response to cold or emotional stimuli, often accompanied by pain.<sup>86</sup>

In terms of thermoregulation, patients with Raynaud phenomenon appear to exhibit lower finger skin blood flow in neutral, cold, and warm environments compared with healthy controls.<sup>87</sup> However, the details of neural control alterations in these patients remain unclear. Local adrenergic mechanisms probably contribute, including up-regulation or sensitization of postsynaptic  $\alpha$ -receptors in the digits (particularly  $\alpha_2$ -receptors).<sup>86</sup> Endothelium-dependent vasodilation in finger skin is significantly impaired in these patients.<sup>88</sup> Increased endothelin 1, a potent endothelium-derived vasoconstrictor, and decreased localized vasodilation mediated by CGRP may also be involved.<sup>89</sup>

Erythromelalgia is a condition of intermittent erythema of peripheral acral skin associated with the sensation of burning pain.<sup>90,91</sup> The pathophysiological features of this condition are poorly understood. The role of neurogenic inflammation has not been investigated extensively. Erythromelalgia appears to involve distal small fiber neuropathy; both sudomotor and peripheral adrenergic function may be impaired.<sup>90,92</sup> Data from recent studies suggest that patients with erythromelalgia have lower baseline skin perfusion (patients did not have symptoms at the time of testing) than healthy subjects in the pulp of the toe and that this area of skin showed less vasoconstriction in response to reflex stimulation of the adrenergic vasoconstrictor system.<sup>93,94</sup> Furthermore, local temperatures between 28°C and 44°C elicited consistently lower skin blood flow responses in patients with erythromelalgia compared with controls.<sup>94</sup> Based on our current understanding of brief local warming,<sup>59,63,70</sup> this finding would be consistent with reduced vascular density, decreased sensory nerve–mediated vasodilation, or some combination thereof. It is difficult to say to what extent vascular control mechanisms measured “between attacks” in these studies<sup>93,94</sup> are relevant to vascular and/or neural dysfunction during the painful intermittent erythema experienced by these patients. Nonetheless, these recent data suggest reflex sympathetic dysfunction and impaired local vasodilator responsiveness, at least in the basal state, in these patients.

### SUMMARY

Skin blood flow can reach high levels during thermal stress, approaching 6 to 8 L/min with severe hyperthermia.

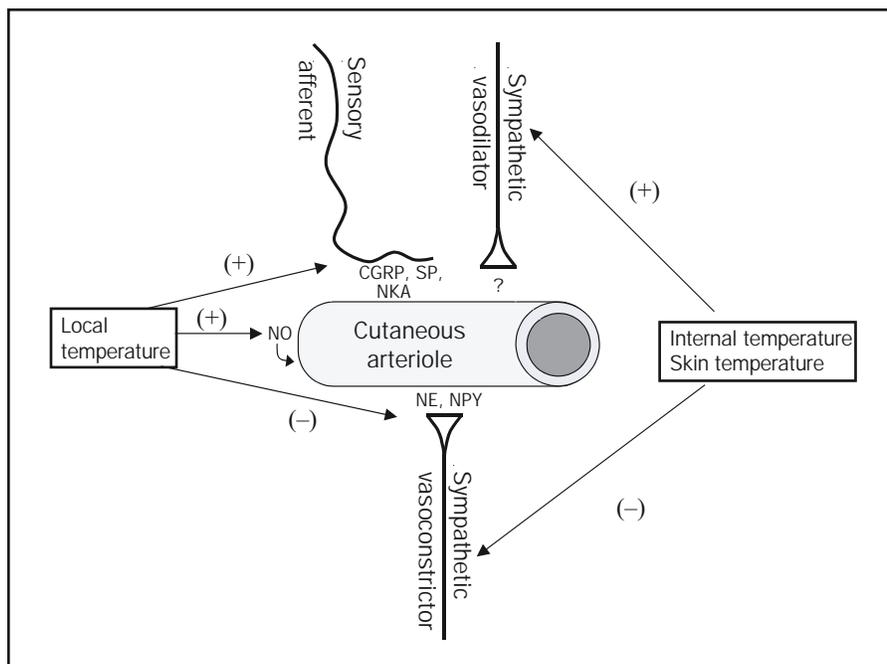


Figure 4. Overview of thermoregulatory control of skin blood flow. Reflex innervation includes sympathetic vasoconstrictor nerves, which release norepinephrine (NE) and 1 or more cotransmitters such as neuropeptide Y (NPY), and active vasodilator nerves, which release an unknown neurotransmitter(s) to cause vasodilation. Local increases in temperature cause vasodilation by stimulating local neuropeptide release from sensory nerves (including calcitonin gene-related peptide [CGRP], substance P [SP], and neurokinin A [NKA]) and by nonneural local vasodilation caused by nitric oxide (NO). Local cooling stimulates localized neurotransmission from noradrenergic nerves to cause vasoconstriction. Plus signs refer to positive relationships: increases in temperature cause increases in activity and vice versa. Minus signs refer to inverse relationships: increases in temperature cause decreases in activity and vice versa.

Thermoregulatory control of the skin circulation in humans represents a set of physiological control mechanisms that are vital to the maintenance of thermal homeostasis. Despite abundant studies during the past several decades, misconceptions persist regarding some of these mechanisms. The local and reflex thermoregulatory control mechanisms discussed in this review are summarized in Figure 4. Current understanding of skin blood flow control includes important roles for both reflex (whole body) and locally mediated cutaneous vasodilation and vasoconstriction. Mechanisms for reflex control of skin blood flow include sympathetic adrenergic vasoconstrictor nerves and sympathetic vasodilator nerves, the latter of which are responsible for 80% to 90% of the substantial cutaneous vasodilation during whole body heat stress. Cutaneous sympathetic vasoconstrictor and active vasodilator systems also participate in blood pressure regulation via the baroreflex, such that the participation of one or the other system depends on the thermal status of the subject. Local thermal control of skin blood flow includes important roles for local adrenergic activity, sensory nerves, and nitric oxide.

Several of these control mechanisms have been shown to be affected by female reproductive hormone status in young premenopausal women and in perimenopausal and postmenopausal women. Altered control of the cutaneous vasodilator system contributes to changes in thermoregulatory control during the menstrual cycle in young women and to differences in thermoregulation between menopausal women undergoing and not undergoing hormone replacement therapy. Further understanding of mechanisms such as these will provide important insight into phenomena such as hot flashes that decrease quality of life in this population.

Circulatory impairments in individuals with type 2 DM appear to include decreases in vasodilator responsiveness in the skin, but the mechanisms involved are unknown. Indirect evidence from epidemiological studies suggests impaired thermoregulation in the heat.<sup>6,7</sup> In this context, impaired thermoregulatory vasodilation during exposure to high ambient temperatures could be due to changes in local thermal control of vasodilation or to altered function of the sympathetic vasodilator and/or vasoconstrictor systems in the skin.

Patients with Raynaud phenomenon and erythromelalgia experience painful extremities due to neurovascular dysfunction. The pathophysiology of these conditions is poorly understood but appears to include alterations in local neural mechanisms and other local factors, such as neuropeptides and endothelial vasoactive factors.

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## REFERENCES

- Johnson JM, Proppe DW. Cardiovascular adjustments to heat stress. In: *Handbook of Physiology*. Fregly MJ, Blatteis CM, eds. Section 4: Environmental Physiology. Vol 1. New York, NY: Oxford University Press; 1996:215-243.
- Taylor WF, Johnson JM, O'Leary D, Park MK. Effect of high local temperature on reflex cutaneous vasodilation. *J Appl Physiol*. 1984; 57:191-196.
- Rowell LB. Cardiovascular adjustments to thermal stress. In: *Handbook of Physiology*. Shepherd JT, Abboud FM, eds. Section 2: The Cardiovascular System. Vol 3, pt 2. Bethesda, Md: American Physiological Society; 1983:967-1023.
- Brooks EM, Morgan AL, Pierzga JM, et al. Chronic hormone replacement therapy alters thermoregulatory and vasomotor function in postmenopausal women. *J Appl Physiol*. 1997;83:477-484.
- Tankersley CG, Nicholas WC, Deaver DR, Mikita D, Kenney WL. Estrogen replacement in middle-aged women: thermoregulatory responses to exercise in the heat. *J Appl Physiol*. 1992;73:1238-1245.
- Schuman SH. Patterns of urban heat-wave deaths and implications for prevention: data from New York and St. Louis during July, 1966. *Environ Res*. 1972;5:59-75.
- Semenza JC, McCullough JE, Flanders WD, McGeehin MA, Lumpkin JR. Excess hospital admissions during the July 1995 heat wave in Chicago. *Am J Prev Med*. 1999;16:269-277.
- Boulant JA. Role of the preoptic-anterior hypothalamus in thermoregulation and fever. *Clin Infect Dis*. 2000;31(suppl 5):S157-S161.
- Boulant JA. Hypothalamic neurons regulating body temperature. In: *Handbook of Physiology*. Fregly MJ, Blatteis CM, eds. Section 4: Environmental Physiology. Vol 1. New York, NY: Oxford University Press; 1996:105-126.
- Pandolf KB, Sawka MN, Gonzalez RR, eds. *Human Performance Physiology and Environmental Medicine at Terrestrial Extremes*. Indianapolis, Ind: Benchmark Press; 1988.
- Handbook of Physiology*. Fregly MJ, Blatteis CM, eds. Section 4: Environmental Physiology. Vol 1. New York, NY: Oxford University Press; 1996.
- Sawka MN, Coyle EF. Influence of body water and blood volume on thermoregulation and exercise performance in the heat. *Exerc Sport Sci Rev*. 1999;27:167-218.
- Young AJ, Castellani JW. Exertion-induced fatigue and thermoregulation in the cold. *Comp Biochem Physiol A Mol Integr Physiol*. 2001;128:769-776.
- Johnson JM. Physical training and the control of skin blood flow. *Med Sci Sports Exerc*. 1998;30:382-386.
- Charkoudian N, Johnson JM. Female reproductive hormones and thermoregulatory control of skin blood flow. *Exerc Sport Sci Rev*. 2000;28:108-112.
- Johnson JM, Brengelmann GL, Hales JR, Vanhoutte PM, Wenger CB. Regulation of the cutaneous circulation. *Fed Proc*. 1986;45:2841-2850.
- Johnson JM. Exercise and the cutaneous circulation. *Exerc Sport Sci Rev*. 1992;20:59-97.
- Roberts MF, Wenger CB, Stolwijk JA, Nadel ER. Skin blood flow and sweating changes following exercise training and heat acclimation. *J Appl Physiol*. 1977;43:133-137.
- Stephenson LA, Kolka MA. Menstrual cycle phase and time of day alter reference signal controlling arm blood flow and sweating. *Am J Physiol*. 1985;249(2, pt 2):R186-R191.
- Aoki K, Stephens DP, Johnson JM. Diurnal variation in cutaneous vasodilator and vasoconstrictor systems during heat stress. *Am J Physiol Regul Integr Comp Physiol*. 2001;281:R591-R595.
- Charkoudian N, Johnson JM. Modification of active cutaneous vasodilation by oral contraceptive hormones. *J Appl Physiol*. 1997; 83:2012-2018.
- Charkoudian N, Johnson JM. Reflex control of cutaneous vasoconstrictor system is reset by exogenous female reproductive hormones. *J Appl Physiol*. 1999;87:381-385.
- Johnson JM, Taylor WF, Shepherd AP, Park MK. Laser-Doppler measurement of skin blood flow: comparison with plethysmography. *J Appl Physiol*. 1984;56:798-803.
- Oberg PA. Laser-Doppler flowmetry. *Crit Rev Biomed Eng*. 1990; 18:125-163.
- Saumet JL, Kellogg DL Jr, Taylor WF, Johnson JM. Cutaneous laser-Doppler flowmetry: influence of underlying muscle blood flow. *J Appl Physiol*. 1988;65:478-481.
- Kellogg DL Jr, Crandall CG, Liu Y, Charkoudian N, Johnson JM. Nitric oxide and cutaneous active vasodilation during heat stress in humans. *J Appl Physiol*. 1998;85:824-829.
- Charkoudian N, Johnson JM. Altered reflex control of cutaneous circulation by female sex steroids is independent of prostaglandins. *Am J Physiol*. 1999;276(5, pt 2):H1634-H1640.
- Johnson JM, Pergola PE, Liao FK, Kellogg DL Jr, Crandall CG. Skin of the dorsal aspect of human hands and fingers possesses an active vasodilator system. *J Appl Physiol*. 1995;78:948-954.
- Lossius K, Eriksen M, Walloe L. Fluctuations in blood flow to acral skin in humans: connection with heart rate and blood pressure variability. *J Physiol*. 1993;460:641-655.
- Stephens DP, Bennett LA, Aoki K, Kosiba WA, Charkoudian N, Johnson JM. Sympathetic nonnoradrenergic cutaneous vasoconstriction in women is associated with reproductive hormone status. *Am J Physiol Heart Circ Physiol*. 2002;282:H264-H272.
- Stephens DP, Aoki K, Kosiba WA, Johnson JM. Nonnoradrenergic mechanism of reflex cutaneous vasoconstriction in men. *Am J Physiol Heart Circ Physiol*. 2001;280:H1496-H1504.
- Hashim MA, Tadepalli AS. Cutaneous vasomotor effects of neuropeptide Y. *Neuropeptides*. 1995;29:263-271.
- Pinter E, Helyes Z, Petho G, Szolcsanyi J. Noradrenergic and peptidergic sympathetic regulation of cutaneous microcirculation in the rat. *Eur J Pharmacol*. 1997;325:57-64.
- Pergola PE, Kellogg DL Jr, Johnson JM, Kosiba WA. Reflex control of active cutaneous vasodilation by skin temperature in humans. *Am J Physiol*. 1994;266(5, pt 2):H1979-H1984.
- Savage MV, Brengelmann GL. Control of skin blood flow in the neutral zone of human body temperature regulation. *J Appl Physiol*. 1996;80:1249-1257.
- Kellogg DL Jr, Johnson JM, Kosiba WA. Selective abolition of adrenergic vasoconstrictor responses in skin by local iontophoresis of bretylium. *Am J Physiol*. 1989;257(5, pt 2):H1599-H1606.
- Pergola PE, Johnson JM, Kellogg DL Jr, Kosiba WA. Control of skin blood flow by whole body and local skin cooling in exercising humans. *Am J Physiol*. 1996;270(1, pt 2):H208-H215.
- Lewis T, Pickering GW. Vasodilation in the limbs in response to warming the body: with evidence for sympathetic vasodilator nerves in man. *Heart*. 1931-1933;16:33-51.
- Grant RT, Holling HE. Further observations on the vascular responses of the human limb to body warming: evidence for sympathetic vasodilator nerves in the normal subject. *Clin Sci*. 1937-1938;3:273-285.
- Edholm OG, Fox RH, Macpherson RK. The effect of body heating on the circulation in skin and muscle. *J Physiol*. 1956;134:612-619.
- Edholm OG, Fox RH, Macpherson RK. Vasomotor control of the cutaneous blood vessels in the human forearm. *J Physiol*. 1957; 139:455-465.
- Roddie IC, Shepherd JT, Whelan RF. The vasomotor nerve supply to the skin and muscle of the human forearm. *Clin Sci*. 1957;16:67-74.
- Roddie IC, Shepherd JT, Whelan RF. Evidence from venous oxygen saturation measurements that the increase in forearm blood flow during body heating is confined to the skin. *J Physiol*. 1956;134:444-450.
- Kellogg DL Jr, Pergola PE, Piest KL, et al. Cutaneous active vasodilation in humans is mediated by cholinergic nerve cotransmission. *Circ Res*. 1995;77:1222-1228.

45. Kolka MA, Stephenson LA. Cutaneous blood flow and local sweating after systemic atropine administration. *Pflugers Arch*. 1987;410:524-529.
46. Shastry S, Minson CT, Wilson SA, Dietz NM, Joyner MJ. Effects of atropine and L-NAME on cutaneous blood flow during body heating in humans. *J Appl Physiol*. 2000;88:467-472.
47. Fox RH, Hilton SM. Sweat gland activity as a contributory factor to heat vasodilation in the human skin. *J Physiol*. 1956;133:68P-69P.
48. Fox RH, Hilton SM. Bradykinin formation in human skin as a factor in heat vasodilatation. *J Physiol*. 1958;142:219-232.
49. Kellogg DL Jr, Johnson JM, Kosiba WA. Control of internal temperature threshold for active cutaneous vasodilation by dynamic exercise. *J Appl Physiol*. 1991;71:2476-2482.
50. Johnson JM, Park MK. Effect of upright exercise on threshold for cutaneous vasodilation and sweating. *J Appl Physiol*. 1981;50:814-818.
51. Kellogg DL Jr, Liu Y, McAllister K, Friel C, Pergola PE. Bradykinin does not mediate cutaneous active vasodilation during heat stress in humans. *J Appl Physiol*. 2002;93:1215-1221.
52. Haeusler G, Haefely W, Huerlimann A. On the mechanism of the adrenergic nerve blocking action of bretylium. *Naunyn-Schmiedeberg's Arch Pharmacol*. 1969;265:260-277.
53. Wallin BG, Sundlof G, Delius W. The effect of carotid sinus nerve stimulation on muscle and skin nerve sympathetic activity in man. *Pflugers Arch*. 1975;358:101-110.
54. Crandall CG, Johnson JM, Kosiba WA, Kellogg DL Jr. Baroreceptor control of the cutaneous active vasodilator system. *J Appl Physiol*. 1996;81:2192-2198.
55. Johnson JM. Nonthermoregulatory control of human skin blood flow. *J Appl Physiol*. 1986;61:1613-1622.
56. Kellogg DL Jr, Johnson JM, Kosiba WA. Baroreflex control of the cutaneous active vasodilator system in humans. *Circ Res*. 1990;66:1420-1426.
57. Rowell LB, Wyss CR, Brengelmann GL. Sustained human skin and muscle vasoconstriction with reduced baroreceptor activity. *J Appl Physiol*. 1973;34:639-643.
58. Tripathi A, Nadel ER. Forearm skin and muscle vasoconstriction during lower body negative pressure. *J Appl Physiol*. 1986;60:1535-1541.
59. Pergola PE, Kellogg DL Jr, Johnson JM, Kosiba WA, Solomon DE. Role of sympathetic nerves in the vascular effects of local temperature in human forearm skin. *Am J Physiol*. 1993;265(3, pt 2):H785-H792.
60. Kellogg DL Jr, Liu Y, Kosiba IF, O'Donnell D. Role of nitric oxide in the vascular effects of local warming of the skin in humans. *J Appl Physiol*. 1999;86:1185-1190.
61. Johnson JM, O'Leary DS, Taylor WF, Kosiba W. Effect of local warming on forearm reactive hyperaemia. *Clin Physiol*. 1986;6:337-346.
62. Charkoudian N, Eisenach JH, Atkinson JL, Fealey RD, Joyner MJ. Effects of chronic sympathectomy on locally mediated cutaneous vasodilation in humans. *J Appl Physiol*. 2002;92:685-690.
63. Minson CT, Berry LT, Joyner MJ. Nitric oxide and neurally mediated regulation of skin blood flow during local heating. *J Appl Physiol*. 2001;91:1619-1626.
64. Holzer P. Neurogenic vasodilatation and plasma leakage in the skin. *Gen Pharmacol*. 1998;30:5-11.
65. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature*. 1997;389:816-824.
66. Xu H, Ramsey IS, Kotecha SA, et al. TRPV3 is a calcium-permeable temperature-sensitive cation channel. *Nature*. 2002;418:181-186.
67. Smith GD, Gunthorpe MJ, Kelsell RE, et al. TRPV3 is a temperature-sensitive vanilloid receptor-like protein. *Nature*. 2002;418:186-190.
68. Peier AM, Reeve AJ, Andersson DA, et al. A heat-sensitive TRP channel expressed in keratinocytes. *Science*. 2002;296:2046-2049.
69. Southall MD, Li T, Gharibova LS, Pei Y, Nicol GD, Travers JB. Activation of epidermal vanilloid receptor-1 induces release of proinflammatory mediators in human keratinocytes. *J Pharmacol Exp Ther*. 2003;304:217-222.
70. Stephens DP, Charkoudian N, Benevento JM, Johnson JM, Saumet JL. The influence of topical capsaicin on the local thermal control of skin blood flow in humans. *Am J Physiol Regul Integr Comp Physiol*. 2001;281:R894-R901.
71. Vanhoutte PM, Cooke JP, Lindblad LE, Shepherd JT, Flavahan NA. Modulation of postjunctional alpha-adrenergic responsiveness by local changes in temperature. *Clin Sci (Lond)*. 1985;68(suppl 10):121s-123s.
72. Flavahan NA, Lindblad LE, Verbeuren TJ, Shepherd JT, Vanhoutte PM. Cooling and alpha 1- and alpha 2-adrenergic responses in cutaneous veins: role of receptor reserve. *Am J Physiol*. 1985;249(5, pt 2):H950-H955.
73. Charkoudian N, Stephens DP, Pirkle KC, Kosiba WA, Johnson JM. Influence of female reproductive hormones on local thermal control of skin blood flow. *J Appl Physiol*. 1999;87:1719-1723.
74. Stephenson LA, Kolka MA. Esophageal temperature threshold for sweating decreases before ovulation in premenopausal women. *J Appl Physiol*. 1999;86:22-28.
75. Silva NL, Boulant JA. Effects of testosterone, estradiol, and temperature on neurons in preoptic tissue slices. *Am J Physiol*. 1986;250(4, pt 2):R625-R632.
76. Brooks-Asplund EM, Kenney WL. Chronic hormone replacement therapy does not alter resting or maximal skin blood flow. *J Appl Physiol*. 1998;85:505-510.
77. Ganz P. Vasomotor and vascular effects of hormone replacement therapy. *Am J Cardiol*. 2002;90(1A):11F-16F.
78. Arora S, Smakowski P, Frykberg RG, et al. Differences in foot and forearm skin microcirculation in diabetic patients with and without neuropathy. *Diabetes Care*. 1998;21:1339-1344.
79. Veves A, Akbari CM, Primavera J, et al. Endothelial dysfunction and the expression of endothelial nitric oxide synthetase in diabetic neuropathy, vascular disease, and foot ulceration. *Diabetes*. 1998;47:457-463.
80. Caballero AE, Arora S, Saouaf R, et al. Microvascular and macrovascular reactivity is reduced in subjects at risk for type 2 diabetes. *Diabetes*. 1999;48:1856-1862.
81. Magerl W, Treede RD. Heat-evoked vasodilatation in human hairy skin: axon reflexes due to low-level activity of nociceptive afferents. *J Physiol*. 1996;497(pt 3):837-848.
82. Hilsted J, Low PA. Diabetic autonomic neuropathy. In: Low PA, ed. *Clinical Autonomic Disorders: Evaluation and Management*. 2nd ed. Philadelphia, Pa: Lippincott-Raven Publishers; 1997:487-507.
83. Low PA, Walsh JC, Huang CY, McLeod JG. The sympathetic nervous system in diabetic neuropathy: a clinical and pathological study. *Brain*. 1975;98:341-356.
84. Fealey RD, Low PA, Thomas JE. Thermoregulatory sweating abnormalities in diabetes mellitus. *Mayo Clin Proc*. 1989;64:617-628.
85. Benarroch EE, Low PA. The acetylcholine-induced flare response in evaluation of small fiber dysfunction. *Ann Neurol*. 1991;29:590-595.
86. Wigley FM, Flavahan NA. Raynaud's phenomenon. *Rheum Dis Clin North Am*. 1996;22:765-781.
87. Greenstein D, Gupta NK, Martin P, Walker DR, Kester RC. Impaired thermoregulation in Raynaud's phenomenon. *Angiology*. 1995;46:603-611.
88. Khan F, Belch JJ. Skin blood flow in patients with systemic sclerosis and Raynaud's phenomenon: effects of oral L-arginine supplementation. *J Rheumatol*. 1999;26:2389-2394.
89. Bunker CB, Goldsmith PC, Leslie TA, Hayes N, Foreman JC, Dowd PM. Calcitonin gene-related peptide, endothelin-1, the cutaneous microvasculature and Raynaud's phenomenon. *Br J Dermatol*. 1996;134:399-406.
90. Sandroni P, Davis MD, Harper CM, et al. Neurophysiologic and vascular studies in erythromelalgia: a retrospective analysis. *J Clin Neuromuscular Dis*. 1999;1:57-63.
91. Davis MD, O'Fallon WM, Rogers RS III, Rooke TW. Natural history of erythromelalgia: presentation and outcome in 168 patients. *Arch Dermatol*. 2000;136:330-336.
92. Davis MD, Rooke TW, Sandroni P. Mechanisms other than shunting are likely contributing to the pathophysiology of erythromelalgia [letter]. *J Invest Dermatol*. 2000;115:1166-1167.
93. Littleford RC, Khan F, Belch JJ. Impaired skin vasomotor reflexes in patients with erythromelalgia. *Clin Sci (Lond)*. 1999;96:507-512.
94. Mork C, Kalgaard OM, Kvernebo K. Impaired neurogenic control of skin perfusion in erythromelalgia. *J Invest Dermatol*. 2002;118:699-703.