Thermoregulatory reflexes and cutaneous active vasodilation during heat stress in hypertensive humans


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Kellogg, D. L., J r., S. R. Morris, S. B. Rodriguez, Y. Liu, M. Grossmann, G. Stagni, and A. M. M. Shepherd. Thermoregulatory reflexes and cutaneous active vasodilation during heat stress in hypertensive humans. J. Appl. Physiol. 85(1): 175–180, 1998.—During dynamic exercise in the heat, increases in skin blood flow are attenuated in hypertensive subjects when compared with normotensive subjects. We studied responses to passive heat stress (water-perfused suits) in eight hypertensive and eight normotensive subjects. Forearm blood flow was measured by venous-occlusion plethysmography, mean arterial pressure (MAP) was measured by Finapres, and forearm vascular conductance (FVC) was calculated. Bretylium tosylate (BT) iontophoresis was used to block active vasoconstriction in a small area of skin. Skin blood flow was indexed by laser-Doppler flowmetry at BT-treated and untreated sites, and cutaneous vascular conductance was calculated. In normothermia, FVC was lower in hypertensive than in normotensive subjects (P < 0.01). During heat stress, FVC rose to similar levels in both groups (P > 0.80); concurrent cutaneous vascular conductance increases were unaffected by BT treatment (P > 0.60). MAP was greater in hypertensive than in normotensive subjects during normothermia (P < 0.05, hypertensive vs. normotensive subjects). During hyperthermia, MAP fell in hypertensive subjects but showed no statistically significant change in normotensive subjects (P < 0.05, hypertensive vs. normotensive subjects). The internal temperature at which vasodilation began did not differ between groups (P > 0.80). FVC is reduced during normothermia in unmedicated hypertensive subjects; however, they respond to passive heat stress in a fashion no different from normotensive subjects.

The role of the human cutaneous circulation in thermoregulatory reflexes is well established. During heat stress, rising internal and skin temperatures (Tsk) induce a reflex cutaneous vasodilation. Similarly, during cold stress, falling temperatures induce cutaneous vasoconstriction. These changes in skin blood flow (SkBF) are controlled by both neural and local factors.

In nonapical areas of human skin, reflex alterations of SkBF are mediated by sympathetic efferent nerves of two types: active vasoconstrictor nerves and active vasodilator nerves (6, 21). Cutaneous vasoconstrictor nerves are noradrenergic and act through postjunctional α1- and α2-receptors (21). This system is activated during periods of cold stress to reduce SkBF and conserve body heat. Cutaneous active vasodilation is effected by a cholinergic cotransmitter system (15). This system is activated during periods of heat stress to increase SkBF and reduce body temperature in conjunction with sweating. Studies of thermoregulatory reflexes in resting normotensive subjects have shown that, during heat stress, there is an initial abolition of any extant vasoconstrictor tone. As internal temperature increases further, the active vasodilator system is activated. The active vasodilator system is responsible for 80–95% of the elevation in SkBF that accompanies heat stress (21).

Hypertension is characterized by an elevated peripheral resistance and is accompanied by a variety of peripheral circulatory changes, including hypertrophy of vascular smooth muscle (2) and vascular rarefaction (3). Carberry et al. (1) reported that hypertension reduces the maximal cutaneous vasodilation induced by local warming of the forearm skin, thus demonstrating that hypertension-induced circulatory changes occur in the skin vasculature. Given this finding, one might expect the thermoregulatory increase in SkBF during hyperthermia to be attenuated in hypertension. In support of this, O’Leary and Wang (19) compared the tail-skin vasodilator responses to passive body heating in spontaneously hypertensive rats (SHR) with that in normotensive Wistar-Kyoto rats. They found that the tail vasodilation during hyperthermia was attenuated in SHR when compared with Wistar-Kyoto rats, thus demonstrating that thermoregulatory vasodilation was impaired in SHR.

In human subjects, Kenney et al. (16, 17) found that the increases in forearm blood flow (FBF) during periods of rising internal temperature induced by dynamic exercise were markedly reduced in hypertensive subjects; hypertensive subjects showed little change in FBF, whereas normotensive subjects showed a fourfold or greater elevation during hyperthermia induced by exercise. Elevation of FBF during leg exercise is confined to the skin (8). The results of Kenney et al. (16, 17) thus suggest that hypertension attenuates increases in SkBF during thermoregulatory-reflex responses to heat stress; however, their studies employed dynamic exercise as the method of raising internal temperature. Thus their studies involved the integrated response of simultaneous nonthermoregulatory (exercise) and thermoregulatory (heat-stress) reflexes. Dynamic exercise induces a nonthermoregulatory-reflex increase in active vasoconstrictor tone that competes with a thermoregulatory-reflex increase in active vasodilator tone originating from heat production associated with exercise (12–14, 21). Because of this confounding nonthermoregulatory effect of exercise, it is not clear whether the mechanism for the attenuated rise in SkBF in hypertensive subjects as observed by Kenney et al. (16,
is due to hypertension-induced alteration of thermoregulatory or nonthermoregulatory reflexes. Hypertensive subjects could have an exaggerated, nonthermoregulatory-reflex vasoconstrictor response to exercise or an attenuated, thermoregulatory vasodilator-reflex response to heat stress.

In addition to these confounding effects, as previously alluded to, in nonapical areas of human skin, control of SkBF is mediated by dual sympathetic efferent neural systems: an active vasodilator system and an active vasoconstrictor system. This dual innervation has made it difficult to identify which individual neural system is responsible for a reflex change in SkBF. It is possible that attenuated increases of SkBF in hypertensive subjects could have an exaggerated, nonthermoregulatory vasoconstrictor response to exercise, as well as the relationship of FVC to Tsl, were analyzed within groups by ANOVA. Internal temperature thresholds (the level of Tsl at which CVC began to rise during whole body heating) were chosen from plots of CVC vs. Tsl by an investigator blinded to the conditions, subjects, and drug treatments involved. These responses, as well as the relationship of FVC to Tsl, were analyzed by ANOVA. The vasomotor responses to cold stress and heat stress were analyzed within groups by ANOVA, which compared the levels of CVC at treated and untreated sites during the initial control period with the levels achieved during the final minute of cold stress and heat stress. Statistical significance was accepted when P < 0.05.

METHODS

Eight hypertensive subjects (all men) and eight normotensive subjects (7 men and 1 woman) participated in this study. All hypertensive subjects were being treated with antihypertensive medications at the time of enrollment. These medications were stopped at least 1 wk before participation in the laboratory protocol. All subjects were documented to be in good health by physical examination and electrocardiogram before their informed consent was obtained to participate in these institutionally approved studies. In the supine position, hypertensive subjects had a mean arterial pressure (MAP) of 116.6 ± 6.5 (SE) mmHg after 1 wk off medications, and normotensive subjects had an average MAP of 93 ± 3 mmHg (P < 0.01, hypertensive vs. normotensive subjects). The two groups were matched for age (hypertensive subjects, 46.5 ± 3.5 yr; normotensive subjects, 47.0 ± 3.2 yr), weight (hypertensive subjects, 80.5 ± 6.7 kg; normotensive subjects, 83.8 ± 7.7 kg), and height (hypertensive subjects, 175 ± 3.9 cm; normotensive subjects, 177 ± 3.5 cm).

Whole body heat stress was induced as follows. Subjects wore a tube-lined suit, which was used to control Tsk by perfusion with water of different temperatures (5, 22). Over the suit, subjects wore a water-impermeable plastic garment to insulate them from room temperature. The suit and garment covered the entire body except for the head, arms, and feet. The suit was perfused with warm water to raise Tsk to 38–39°C during heating periods and with cold water to lower Tsk from 34–35.5°C to 31.5–32°C during cold stress.

Internal temperature was monitored with a thermocouple placed in the sublingual sulcus (Tsl). Tsk was measured as the weighted electrical average from six thermocouples taped on the skin surface (5, 22). MAP and pulse rate were recorded continuously from a finger (Finapres blood pressure monitor, Ohmeda, Madison, WI; Ref. 18). FBF was measured by using venous-occlusion plethysmography. This technique provides a measurement of absolute FBF (combined SkBF and muscle blood flow) and thus can be used for comparisons between groups. Forearm vascular conductance (FVC) was calculated as FBF/MAP.

On the contralateral arm from plethysmography measurements, laser-Doppler blood flow (LDF; MBF3D dual-channel flowmeter, Moor Instruments, Devon, UK) from skin was measured simultaneously at two forearm sites. At one of these sites, active vasoconstrictor control in a small area of skin (0.64 cm²) was selectively abolished by the iontophoresis of bretylium (4, 10). The advantage of a local application of bretylium was the avoidance of any systemic drug effects. LDF was monitored from the bretylium-treated and control sites. The key to this approach is that the presynaptic blockade of norepinephrine release by bretylium blocks the vasoconstrictor system and leaves the active vasodilator system unaltered. Body cooling was used to produce cold stress to verify blockade of the active vasodilator system. Body heating was used to produce heat stress and to activate the vasodilator system. LDF measurements are specific to skin and are uninfluenced by blood flow in the underlying tissues (23). LDF does not provide absolute measurements of flow and thus cannot be used for comparisons between groups in which baseline differences are likely, i.e., normotensive and hypertensive subjects (1, 9). However, LDF measurements in combination with iontophoresis of bretylium provide indexes of vasoconstrictor and vasodilator tones that can be compared within groups. For these comparisons, cutaneous vascular conductance (CVC) was calculated as LDF (in V)/MAP (in mmHg).

Special LDF probe holders were used to permit simultaneous measurement of LDF and control of local temperature (Tloc) at the sites of LDF measurement. The LDF probe head was placed in a central chamber in the probe holder. Local warming was accomplished by use of resistive heating elements embedded within the probe holder. A thermocouple was placed between the skin surface and the probe holder to provide measurement of Tloc and feedback for temperature control.

In the protocol, the two groups were subjected to similar temperatures during passive normothermia, hypothermia, and hyperthermia. All subjects were studied in the supine position to minimize potentially confounding baroreflex effects (11, 14). Data collection began with a 5-min normothermic control period followed by a 3-min application of whole body cold stress to verify that vasoconstrictor nerve function was blocked and that bretylium pretreatment had not had unanticipated effects on either nerve or vascular function. After a few minutes of recovery, Tsk was raised to 38–39°C and was maintained at that level for 35–45 min to induce heat stress. After hyperthermia, subjects were cooled to normothermia. Finally, Tloc values at both LDF sites were raised to 42°C to measure maximal vasodilation (7, 24). For LDF data analysis, CVC values were normalized to those maximal levels (14). Data are presented as means ± SE. Quantitative comparisons between groups were made for Tsl, Tsk, MAP, and FVC by ANOVA. Internal temperature thresholds (the level of Tsl at which CVC began to rise during whole body heating) were chosen from plots of CVC vs. Tsl by an investigator blinded to the conditions, subjects, and drug treatments involved. These responses, as well as the relationship of FVC to Tsl, were analyzed by ANOVA. The vasomotor responses to cold stress and heat stress were analyzed within groups by ANOVA, which compared the levels of CVC at treated and untreated sites during the initial control period with the levels achieved during the final minute of cold stress and heat stress. Statistical significance was accepted when P < 0.05.
RESULTS

Normothermic FVC values were much lower in the hypertensive group (0.028 ± 0.002 vs. 0.064 ± 0.005 ml·100 ml⁻¹·min⁻¹·mmHg⁻¹, hypertensive vs. normotensive; P < 0.01 between groups). FVC fell significantly in normotensive subjects during cold stress to 0.038 ± 0.004 ml·100 ml⁻¹·min⁻¹·mmHg⁻¹ (P < 0.05 vs. normothermia) but showed no significant fall in hypertensive subjects (0.028 ± 0.004 ml·100 ml⁻¹·min⁻¹·mmHg⁻¹, P > 0.80 vs. normothermia). During peak cold stress, these FVC values did not differ between groups (P > 0.10). Finally, no significant differences were found in FVC at the peak of passive heat stress (0.132 ± 0.015 vs. 0.137 ± 0.019 ml·100 ml⁻¹·min⁻¹·mmHg⁻¹, normotensive vs. hypertensive; P > 0.80 between groups). FVC results are summarized in Fig. 1.

During normothermia, the mean CVC [expressed as %maximal vasodilation induced by local heating to 42°C (%max)] for the hypertensive group was 20 ± 8%max at the bretylium-treated site and 24 ± 8%max at the untreated site (P > 0.30), and, for the normotensive group, it was 17 ± 3%max at the bretylium-treated site and 23 ± 6%max at the untreated site (P > 0.60). Thus bretylium treatment did not significantly alter the CVC in either the normotensive or hypertensive group during the normothermic control period (see Fig. 2).

Blockade of active vasoconstriction at the bretylium-treated site was verified by measurement of the reduction in CVC during cold stress. During cold stress in the hypertensive group, the untreated site fell from 20 ± 8 to 8 ± 2%max CVC (P < 0.01), whereas the sites that received bretylium iontophoresis were statistically unchanged from normothermic levels (23 ± 8%max in normothermia; 16 ± 4%max in cold stress, P > 0.05). In the normotensive group, CVC at the untreated site fell from 17 ± 3 to 12 ± 2%max CVC (P < 0.05), whereas the sites that received bretylium were statistically unchanged (23 ± 6%max in normothermia; 22 ± 4%max in cold stress, P > 0.05). Bretylium iontophoresis thus blocked vasoconstriction in both the normotensive and hypertensive groups during cold stress.

During heat stress in hypertensive subjects, CVC at the untreated sites rose to 73 ± 6%max and at bretylium-treated sites to 74 ± 6%max (P > 0.90 between sites). In normotensive subjects, CVC rose to 91 ± 9%max CVC at untreated sites and to 86 ± 11%max CVC at bretylium-treated sites (P > 0.90 between sites). In normotensive subjects, CVC rose to 91 ± 9%max CVC at untreated sites and to 86 ± 11%max CVC at bretylium-treated sites (P > 0.30 between sites). *P < 0.05: untreated group under normothermic vs. cold-stress condition; untreated vs. bretylium-treated group under cold-stress condition.

*P < 0.05 normotensive group under normothermic vs. cold-stress condition; **P < 0.01 normotensive vs. hypertensive group under normothermic condition.
untreated sites rose to 91 ± 9%max and at the bretylium-treated site to 86 ± 11%max (P > 0.30 between sites).

In contrast with blood flow results, MAP changed significantly during peak heat stress. During normothermia, hypertensive subjects had a MAP of 116 ± 6 mmHg, whereas normotensive subjects had a MAP of 93 ± 5 mmHg (P < 0.01). During heat stress, MAP in hypertensive subjects significantly fell to 103 ± 5 mmHg (P < 0.05), whereas normotensive subjects showed no significant change in MAP. MAP values for the hypertensive and normotensive subjects were not significantly different during peak heat stress (104 ± 4 and 102 ± 5 mmHg, respectively; P > 0.20 between groups).

Under normothermic conditions, both the hypertensive and normotensive groups had similar Tsk values (33.4 ± 0.4 and 33.8 ± 0.7°C, respectively; P > 0.50) and Tsl values (36.65 ± 0.14 and 36.64 ± 0.09°C, respectively; P > 0.90). The Tsl threshold at which cutaneous vasodilation began was compared 1) between the hypertensive and normotensive groups, 2) within each group between the bretylium-treated and untreated sites, and 3) between groups by site. No significant difference existed between hypertensive and normotensive subjects by sites (P > 0.30) or by groups (P > 0.40) (see Fig. 3). Tsl rose significantly in both groups from normothermic levels to peak heat-stress levels (P < 0.05, normothermia vs. heat stress in both groups). At peak heat stress, Tsl values were not significantly different between the hypertensive and normotensive groups (37.44 ± 0.17 and 37.30 ± 0.09°C; P > 0.40; see Fig. 4). No differences were found in the relationship of FVC with internal temperature during heat stress between groups (0.107 ± 0.033 vs. 0.162 ± 0.040 ml·100 ml⁻¹·min⁻¹·mmHg⁻¹·°C⁻¹, normotensive vs. hypertensive; P > 0.30 between groups).

**DISCUSSION**

We have shown that thermoregulatory responses to passive heat stress are unaltered in our hypertensive subjects. During heat stress, both hypertensive and normotensive subjects began to vasodilate at similar internal temperatures. Internal temperature and FVC both rose to similar levels at the peak of heat stress in the two groups. The sensitivity of FVC to Tsl changes, i.e., the relationship of FVC increases with internal temperature increases, did not differ between the groups. CVC values at BT-treated sites (with active vasodilator control only) and untreated sites (with both vasoconstrictor and vasodilator controls intact) were not different within groups during heat stress, revealing that the neural mechanism effecting increased SkBF was not altered in hypertensive subjects, i.e., no increased vasoconstrictor tone was present during hyperthermia in hypertensive subjects. From the above results, we conclude that unmedicated hypertensive and normotensive subjects respond to passive heat stress in a similar way. This conclusion is based on the quantitatively and qualitatively similar responses of normotensive and hypertensive subjects during hyperthermia.

Although our CVC data showed no evidence that active vasoconstrictor tone was present during heat stress in hypertensive subjects, we did find a sugges-

![Fig. 3. Summary of internal temperature threshold results (means ± SE).](https://example.com/fig3)

![Fig. 4. Summary of internal temperatures during normothermia and heat stress (means ± SE). In hypertensive subjects under normothermic conditions, internal temperature averaged 36.64 ± 0.14°C and rose to 37.44 ± 0.17°C during heat stress (P < 0.01, normothermia vs. heat stress). In normotensive subjects under normothermic conditions, internal temperature averaged 36.65 ± 0.09°C and rose to 37.30 ± 0.09°C during heat stress (P < 0.01, normothermia vs. heat stress). No significant difference existed between hypertensive and normotensive subjects under normothermic or heat-stress conditions (P > 0.40).](https://example.com/fig4)
tion that increases in active vasodilator tone could be augmented in hypertensive subjects during heat stress. Bretylium blockade of the active vasoconstrictor system did not alter the CVC increase during hyperthermia in either normotensive or hypertensive subjects, indicating that all of the increase in SkBF during heat stress was mediated by increased active vasodilator tone (see Fig. 2). During normothermia, FVC levels were lower in hypertensive than in normotensive subjects. Because FVC rose to similar levels in both groups during heat stress, the quantitative FVC increases from normothermic levels in hypertensive subjects significantly exceeded those in normotensive subjects (see Fig. 1). Taken together, the greater quantitative FVC increase suggests that thermoregulatory-reflex-mediated increases in active vasodilator tone could have been greater in hypertensive than in normotensive subjects. However, because we found no difference in the sensitivity of FVC to increases in Tsi,w, we are unable to draw a firm conclusion.

Under normothermic conditions, FVC levels (with both muscle and skin components) were reduced in hypertensive subjects when compared with normotensive subjects, consistent with other studies of hypertensive subjects (1). Comparisons of the CVC data (which are specific to skin) within the hypertensive and normotensive groups in normothermia revealed no differences between BT-treated and untreated sites. BT treatment abolishes local noradrenergic vasoconstrictor control mechanisms that remain intact at untreated sites. Thus our CVC data indicate that, under normothermic conditions, cutaneous noradrenergic vasoconstrictor tone is not elevated in hypertensive subjects in the supine position. This suggests that the reduced FVC (with both muscle and skin components) during normothermia was due to other mechanisms altered by hypertension, such as 1) structural alterations of the forearm vasculature, 2) enhanced vasoconstrictor tone directed to skeletal muscle vasculature only, 3) enhanced forearm vasoconstriction due to attenuated nitric oxide or other endothelium-derived relaxing factor mechanisms, or 4) enhanced endothelin or other endothelium-derived contracting factor-mediated vasoconstrictor effects.

During cold stress, CVC at BT-treated sites was unchanged from normothermic levels in both normotensive and hypertensive subjects, verifying blockade of noradrenergic active vasoconstriction. During cold stress at untreated sites, CVC fell in both groups, qualitatively demonstrating that vasoconstrictor tone increased in hypertensive subjects just as it did in normotensive subjects. However, as illustrated in Fig. 1, quantitative changes in FVC during cold stress were minimal in the hypertensive subjects. This is primarily a function of the vasoconstricted state of the forearm vasculature in hypertensive subjects under normothermic conditions. This suggests that, although cutaneous noradrenergic vasoconstrictor tone increases during cold exposure, little further reduction of SkBF can be accomplished beyond the already low levels present in normothermia in hypertensive subjects. Thus hypertensive subjects appear to have little effective vasoconstrictor reserve in the cutaneous vasculature, perhaps because of the mechanisms suggested above.

Kenney et al. (16, 17) showed that, during dynamic exercise in a semireclining position, hypertensive subjects showed a greatly attenuated rise in FBF as internal temperature increased, when compared with normotensive subjects. It is clear that in normotensive subjects the reflex adaptations to dynamic exercise include the simultaneous activation of the cutaneous vasoconstrictor system by exercise, which competes with active vasodilator drive evoked by the heat production associated with exercise. The result of this competition is an attenuated increase in SkBF as internal temperature rises and a reduced absolute increase of SkBF, when compared with heat stress alone (13, 14). Thus the responses to dynamic exercise represent an integrated response between simultaneous thermoregulatory and nonthermoregulatory reflexes. Given the present results that thermoregulatory vasodilator responses to heat stress are preserved, the results of Kenney et al. (16, 17) suggest that exercise evokes an exaggerated increase in vasoconstrictor tone in hypertension. Thus it appears that hypertension alters nonthermoregulatory reflexes but leaves thermoregulatory-reflex responses to heat stress essentially intact.

Could other nonthermoregulatory reflexes account for the differences between our results and those of Kenney et al. (16, 17)? We have shown in normotensive subjects that the active vasodilator system is affected by unloading of the baroreflex. For example, during hyperthermia in the supine position, SkBF is reduced during baroreflex unloading by lower body negative pressure (11, 14). Could the semireclining posture used in the studies of Kenney et al. (16, 17) have limited active vasodilation to a greater extent in hypertensive subjects? In the present study, we found that, during hyperthermia, FVC responses were preserved in hypertensive subjects, but MAP fell. MAP was unchanged in normotensive subjects during heat stress. Whereas it should be noted that some studies report that blood pressure can fall by ~10% in normotensive subjects during hyperthermia (5), our results, consistent with other studies (20), suggest that nonthermoregulatory-baroreflex responses are attenuated during passive heat stress in hypertensive subjects.

In summary, we found that, although FBF was reduced in normothermia in hypertensive subjects, thermoregulatory-reflex responses of the cutaneous vasculature to passive hyperthermia were not attenuated. This suggests that attenuation of SkBF responses to prolonged dynamic exercise in hypertensive subjects is due to exaggeration of cutaneous active vasoconstrictor tone by nonthermoregulatory exercise reflexes rather than to attenuated active vasodilation. We conclude that unmedicated hypertensive subjects respond to passive heat stress in a fashion similar to normotensive subjects.
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