Reflex control of the cutaneous circulation during passive body core heating in humans

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Peters, Jochen K., Takeshi Nishiyasu, and Gary W. Mack. Reflex control of the cutaneous circulation during passive body core heating in humans. J Appl Physiol 88: 1756–1764, 2000.—The impact of body core heating on the interaction between the cutaneous and central circulation during blood pressure challenges was examined in eight adults. Subjects were exposed to –10 to –90 mmHg lower body negative pressure (LBNP) in thermoneutral conditions and –10 to –60 mmHg LBNP during heat stress. We measured forearm vascular conductance (FVC; ml·min⁻¹·100 ml⁻¹·mmHg⁻¹) by plethysmography; cutaneous vascular conductance (CVC) by laser-Doppler techniques; and central venous pressure, arterial blood pressure, and cardiac output by impedance cardiography. Heat stress increased FVC from 5.7 ± 0.9 to 18.8 ± 1.3 conductance units (CU) and CVC from 0.21 ± 0.07 to 1.02 ± 0.20 CU. The FVC-CVP relationship was linear over the entire range of LBNP and was shifted upward during heat stress with a slope increase from 0.46 ± 0.10 to 1.57 ± 0.3 CU/mmHg CVP (P < 0.05). Resting CVP was lower during heat stress (6.3 ± 0.6 vs. 7.7 ± 0.6 mmHg; P < 0.05) but fell to similar levels during LBNP as in normothermic conditions. Data analysis indicates an increased capacity, but not sensitivity, of peripheral baroreflex responses during heat stress. Laser-Doppler techniques detected thermoregulatory responses in the skin, but no significant change in CVC occurred during mild-to-moderate LBNP. Interestingly, very high levels of LBNP produced cutaneous vasodilatation in some subjects.

forearm blood flow; baroreceptor; central venous pressure; lower body negative pressure

IN HUMANS, THERMAL STATUS is believed to impact the response of the peripheral circulation to cardiovascular reflexes. For example, during heat stress the relative reduction in forearm vascular conductance (FVC) during orthostatic stress is more pronounced, but the absolute values remain above those levels reached in a normothermic state (2, 7, 13). The interpretation of these data has been consistent. The change in FVC is too large to be solely attributed to vasomotor adjustments in skeletal muscle. Thus a response in the cutaneous circulation has been implicated. However, the dose-response relationship between peripheral and central hemodynamic variables in different thermal conditions has not been defined.

Laser-Doppler velocimetry has been used to specifically examine cutaneous blood flow responses to thermoregulatory and baroreflexes. Studies adopting this method have provided controversial results. Kellogg and co-workers (11) used local iontophoresis of bretylium tosylate for selective presynaptic blockade of the cutaneous α-adrenergic vasoconstrictor system. In normothermic conditions, cutaneous vascular conductance (CVC) was reduced during –40 mmHg lower body negative pressure (LBNP) in the untreated, but not in the treated, skin site. During whole body heating (skin temperature >38°C), LBNP induced equal CVC reductions in both skin sites, suggesting withdrawal of vasodilator tone. Interestingly, after the subjects were returned to normothermia the untreated skin site no longer responded to LBNP. In a similar protocol, Chandall and co-workers (1) examined the relative contribution of the cardiopulmonary and the carotid baroreceptors in the regulation of cutaneous blood flow. Application of –30 mmHg LBNP in normothermic conditions reduced FVC and CVC. When skin temperature was increased to 38°C, application of –5 or –10 mmHg LBNP did not affect CVC but reduced FVC, suggesting that only muscle, but not skin, blood flow had changed. During –30 mmHg LBNP, CVC and FVC were reduced. The protocol was repeated by using pulsatile carotid pressure to selectively unload carotid baroreceptors. This stimulus increased heart rate (HR) and blood pressure, but neither CVC nor FVC responded. These data support the primary role of cardiopulmonary baroreceptors in mediating the change in CVC and FVC during LBNP. In contrast, studies by Ryan et al. (20) suggest a predominant role of arterial baroreceptors in the control of ear blood flow in rabbits. Intact animals and animals with sinoaortic denervation were exposed to whole body heating to maximize vascular conductance in the ear. Neither pharmacological blockade nor mechanical unloading of the low-pressure baroreceptors induced a vasoconstrictor response. However, ramp decreases of arterial blood pressure triggered reductions in ear blood flow in the animals with intact arterial baroreceptors.

In humans, Vissing and co-workers (25) combined laser-Doppler velocimetry with measurements of sympathetic nerve activity to skin and muscle. In normothermia, application of –5, –10, and –15 mmHg LBNP...
increased muscle sympathetic nerve activity without a change in skin sympathetic nerve activity. In heated subjects, application of −15 mmHg LBNP reduced CVC, but these changes were also produced by sham LBNP that created an air current over the lower body but no negative pressure in the LBNP box. The CVC response during sham LBNP was abolished by local skin heating that prevented a drop in skin temperature. In another study, the same group (26) was unable to measure any changes in skin blood flow or sympathetic nerve activity in 13 subjects exposed to 20 min of −50 mmHg LBNP. These observations do not support the concept that the skin participates importantly in baroreceptor-mediated reflexes. In fact, they argue that thermoregulatory reflexes responding to changes in skin temperature mediate the change in skin blood flow during LBNP, when observed. Data from our laboratory (14) show a marked heterogeneity in the skin blood flow response to LBNP within a given 1-cm² area of skin. At present, it is unclear which factors contribute to the observed discrepancy in the CVC response to LBNP.

One potential problem with studies examining the integration of thermoregulatory and baroreflexes is that heat stress is commonly evoked by direct skin heating to nonphysiological temperatures ≥38°C. Under such circumstances, local vascular responses to high temperatures (over the majority of the skin surface) may modify vasoregulatory signals from the central nervous system or the response of effector organs to these signals (17, 21). More importantly, the dominant afferent sensory input into the thermoregulatory control system is body core and not skin temperature. The present study examined the impact of body core temperature on the baroreflex control of skin blood flow at physiological skin temperatures. We were particularly interested in the interaction between the cutaneous and the central circulation and used graded LBNP to very high levels to analyze the dose-response relationship of the evoked changes. Standard plethysmographic measurements of forearm blood flow were combined with laser-Doppler measurements of skin blood flow in an untreated and a bretylium-treated skin site as described by Kellogg et al. (10).

METHODS

Subjects

Eight healthy subjects (nonsmokers: 3 women, 5 men) gave written, informed consent to participate in the study. Their mean (range) physical characteristics were age 32 (24–38) yr, weight 70.3 (55.6–86.4) kg, and height 173.6 (156–191) cm. On a separate day, before the experiment, all subjects were thoroughly familiarized with the experimental procedure. On the day of the experiment, they had a light breakfast but no caffeine-containing drinks. All experiments were conducted in the late morning. The Yale University School of Medicine Human Investigation Committee approved the protocol.

Experimental Protocol

Two hours before the subjects entered the environmental test chamber, two skin sites on the volar side of the left forearm were chosen for measurement of skin blood flow with laser-Doppler velocimetry. Bretylium tosylate was applied locally to the skin by iontophoresis to block transmitter release from sympathetic vasoconstrictor nerve terminals, as described by Kellogg et al. (10). A LectroPatch (General Medical, Los Angeles, CA) iontophoresis unit, consisting of two adjacent yet separate treatment compartments, was used. In each compartment, a 3.1-cm² treatment pad was placed and soaked with 1.5 ml of either bretylium tosylate (100 mM) or vehicle (pure water). The iontophoresis protocol consisted of 20 min at a current density of 160 µA/cm² followed by 20 min at a current density of 80 µA/cm².

Experimental preparation of the subjects occurred within the environmental chamber at an ambient temperature of 28°C. Subjects wore a tubed-lined garment perfused with water at 34°C and lay supine within the LBNP box. Their lower legs were immersed in 34°C water for ~30–45 min during catheter placement and instrumentation. After experimental preparation, subjects were allowed to rest undisturbed for 15 min before baseline measurements were performed. Next, cold stress was applied for a period of 4 min by perfusion of cold (5°C) water through the garment to demonstrate thermoregulatory-mediated reflex cutaneous vasoconstriction at the untreated skin site and effective local vasoconstrictor blockade in the bretylium-treated skin site by using laser-Doppler velocimetry.

After cold stress, the water circulating through the liquid perfusion garment was returned to 34°C, and another 15-min rest period served to return the subjects to thermoneutral conditions. Data were then collected during 2 min of control, 2 min of each level of LBNP, and 2 min of recovery. In the thermoneutral state, LBNP was applied in a graded stepwise fashion by using −10, −20, −30, and −40 mmHg. The higher levels of LBNP, −60, −75, and −90 mmHg, were applied individually. To avoid arousing responses, LBNP was increased slowly over ~30 s before reaching the final level. After the last LBNP level, subjects were then passively heated by raising the lower leg water bath temperature to 44°C. Within 25–30 min, body core temperature (esophageal temperature) had reached a new plateau, and LBNP was repeated in a graded stepwise fashion by using −10, −20, and −30 mmHg LBNP. Higher levels of LBNP (−40 and −60 mmHg) were applied as separate perturbations. To avoid syncope, heated subjects were not exposed to LBNP greater than −60 mmHg. After each experimental episode, baseline conditions were regained during a 10-min rest period during which all catheters were flushed with heparinized saline to maintain patency.

At the end of the experimental procedures, the left forearm was immersed in 44°C water for 20 min to define maximal CVC. Finally, cold stress was repeated when the subjects were vasodilated by heat stress to reconfirm the effectiveness of the local adrenergic blockade. Dehydration during the experiment was prevented by infusing normal saline at a rate of 5 ml · kg⁻¹ · h⁻¹ during thermoneutral and 10 ml · kg⁻¹ · h⁻¹ during heat stress conditions. Saline infusion resulted in a slight weight gain of 100–200 g during the course of the experiment.

Measurements

Thermal stress. Subjects were studied at rest in the supine position, with the lower body enclosed in a negative-pressure chamber that included a temperature-controlled water bath for immersion of the lower legs. The lower legs were immersed in the water bath that was set to 34°C. To control skin temperature over the rest of the body, the subjects wore a liquid-perfused garment that covered the entire body with the exception of the head, both forearms, and both lower legs and

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was perfused with water at 34°C. To examine the impact of cold stress on skin blood flow, the inlet for the water-perfused garment was rapidly switched to a 5°C water bath for 4 min and then returned to 34°C. To raise body core temperature, the water bath within the LBNP box was raised to 44°C.

Body core and skin temperature. Internal body temperature was measured with a thermocouple that was advanced through the nose into the esophagus to approximately the level of the left atrium. Depth of insertion was 25% of the subject’s standing height. Mean skin temperature was recorded as a weighted average from thermocouples placed at seven sites over the body surface: forehead, upper arm, chest, forearm, abdomen, thigh, and calf (15).

Central hemodynamic variables. Central venous pressure (CVP) was measured directly through a 4-Fr catheter, inserted under local anesthesia into the left antecubital vein and advanced to the superior vena cava. Catheter placement was determined from body surface measurements and waveform analysis. CVP was recorded with a Gold Statham P23ID pressure transducer referenced to the midaxillary line. Cardiac stroke volume (SV) was measured noninvasively by impedance cardiology (model 304 B, Minnesota Impedance Cardiograph) from four silver tape electrodes placed around the neck and the torso, by using the equation of Kubicki et al. (12). The impedance signals were recorded continuously and processed as the ensemble average of all the cardiac cycles during each 30-s period. HR was recorded on-line from an electrocardiogram, and cardiac output (CO) was calculated by multiplying HR and SV. Arterial blood pressure was measured beat by beat with a noninvasive finger cuff (Ohmeda 2300 Finapress), and mean arterial pressure (MAP) was calculated from the area under the curve. Systemic vascular conductance was calculated as CO/(MAP – CVP) and expressed as liters per minute per 100 millimeters of Hg.

Forearm blood flow. Forearm blood flow was measured in the right arm by venous occlusion plethysmography (27). The hand and the elbow were comfortably rested on pads elevating the forearm at an angle of −30° from the horizontal plane in an effort to allow free drainage of venous blood. The hand was excluded from the circulation by cuff occlusion of the wrist to 270–300 mmHg. A second pneumatic occlusion cuff, placed 1 cm above the elbow, was rapidly inflated (<1 s) to ~48 mmHg three times per minute to stop venous outflow for 8–10 s. The rate of increase in forearm circumference was measured with a Whitney mercury-in-Silastic strain gauge. Blood flow was calculated from the linear part of the slope of the volume change and expressed as milliliters per 100 milliliters of tissue per minute. FVC was calculated as forearm blood flow/(MAP – CVP) and expressed as milliliters per 100 milliliters tissue per minute per 100 millimeters Hg.

Skin blood flow. Measurements of skin blood flow were performed in the left forearm by using laser-Doppler velocimetry (fioLAB, Moor Instruments). Briefly, a laser beam is transmitted to the skin through an optical fiber at a wavelength of 780 nm, and the reflected signal is returned through another pair of optical fibers to a photodiode. Light reflected from moving red blood cells is shifted to a different wavelength that is converted into a voltage output that is proportional to red blood cell flux. A time constant of 0.1 s was used during recording of laser-Doppler flux data. The laser probes have a sample surface area of ~1 mm² and a penetrating depth of 0.5–1.5 mm. Two such probes were affixed with adhesive rings to the volar forearm in sites without superficial veins that demonstrated high flux values and pulsatile activity. As described in Experimental Protocol, one skin site had been pretreated with bretyllium tosylate. Special care was taken to support the fiber-optic cables and to prevent movements of the arm. CVC was calculated as the laser-Doppler signal output in volts divided by MAP (V/100 mmHg). CVC was expressed in two forms: 1) a percentage of peak CVC and 2) percentage of control. Peak CVC was defined as the CVC during local heating of the left forearm to 43°C for 30 min, and control was defined as the CVC measured before the first application of LBNP in the thermoneutral condition.

Data Acquisition and Analysis

Data were recorded continuously with an eight-channel computerized data-acquisition system and averaged over 30-s periods (MacLab System, ADInstruments). The data used for analysis represent the last 30-s period of control before the initiation of LBNP and the last 30-s period of each level of LBNP. Forearm blood flow was calculated from the slope of the increase in arm circumference per unit time and represents the average of two to four measurements during each level of LBNP. All data are reported as means ± SE.

The comparison of the hemodynamic responses at various levels of LBNP within and between the two thermal conditions was done by a repeated-measures ANOVA. Least squares linear regression was used to describe the functional relationship between two variables. The slopes of the regression lines were compared by paired t-test. Differences were considered significant at P < 0.05.

RESULTS

Cold Stress

Application of cold stress induced a significant reduction in CVC at the untreated skin site before (~28.6 ± 5.4%; P < 0.05) and after (~21.7 ± 3.6%; P < 0.05) the experimental protocol. Iontophoresis of bretylium blocked the cold-induced reduction in CVC before (+8.1 ± 4.9%; P > 0.1) and after heating (~4.9 ± 2.6%; P > 0.1), demonstrating effective and persistent sympathetic vasoconstrictor blockade.

Body Temperature and Hemodynamic Responses to Heat Stress

Esophageal temperature increased from 36.8 ± 0.1 to 37.3 ± 0.1°C (P < 0.05) during heat stress and induced marked sweating in all subjects. Mean skin temperature also increased from 35.2 ± 0.1 to 35.7 ± 0.1°C (P < 0.05). CO increased by 1.3 ± 0.3 l/min because of a 20–24 beats/min increase in HR, whereas cardiac SV was unchanged (Table 1). In the periphery, heat stress induced a more than threefold increase in FVC (from 5.7 ± 0.9 to 18.8 ± 1.3 ml·100 ml tissue−1·min−1·100 mmHg−1). CVC increased from 0.21 ± 0.07 (19.0 ± 3.9% maximum) to 1.02 ± 0.20 CU (108.8 ± 10.0% maximum) and from 0.36 ± 0.13 (10.1 ± 1.5% maximum) to 1.33 ± 0.17 CU (62.7 ± 5.1% maximum) during heat stress in the untreated and treated skin sites, respectively. The increase in CVC during heat stress was smaller in the bretyllium-treated skin site than in the untreated skin site (P < 0.05). Despite the increase in CO, the redistribution of blood flow in the heated state reduced CVP (8.0 ± 0.6 to 6.1 ± 0.6 mmHg) and MAP (91 ± 3 to 80 ± 2 mmHg, P < 0.05).
BAROREFLEX CONTROL OF SKIN BLOOD FLOW

Table 1. Hemodynamic variables at rest and during lower body negative pressure in normothermic and heat stress conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Central Venous Pressure, mmHg</th>
<th>Mean Arterial Pressure, mmHg</th>
<th>Forearm Blood Flow, ml·100 ml tissue·1·min⁻¹</th>
<th>Forearm Vascular Conductance, ml·100 ml tissue⁻¹·min⁻¹·100 mmHg⁻¹</th>
<th>Heart Rate, beats/min</th>
<th>Stroke Volume, ml</th>
<th>Cardiac Output, l·min⁻¹</th>
<th>Systemic Vascular Conductance, l·min⁻¹·100 mmHg⁻¹</th>
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<tbody>
<tr>
<td>Normothermia</td>
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<tr>
<td>Control</td>
<td>8.0 ± 0.6</td>
<td>91.2 ± 2.8</td>
<td>5.3 ± 1.0</td>
<td>6.0 ± 1.0</td>
<td>64.4 ± 2.5</td>
<td>100.4 ± 11.0</td>
<td>6.3 ± 0.5</td>
<td>7.7 ± 0.8</td>
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<td>LBNP</td>
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<tr>
<td>−10 mmHg</td>
<td>4.8 ± 0.6*</td>
<td>91.7 ± 2.9</td>
<td>3.8 ± 0.7*</td>
<td>4.2 ± 0.8*</td>
<td>66.5 ± 3.1</td>
<td>89.2 ± 11.4</td>
<td>5.8 ± 0.6*</td>
<td>6.8 ± 0.7</td>
</tr>
<tr>
<td>−20 mmHg</td>
<td>2.7 ± 0.6*</td>
<td>89.2 ± 2.4</td>
<td>3.2 ± 0.6*</td>
<td>3.6 ± 0.7*</td>
<td>67.6 ± 3.3</td>
<td>81.3 ± 8.8</td>
<td>5.3 ± 0.4</td>
<td>6.2 ± 0.7</td>
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<tr>
<td>−30 mmHg</td>
<td>1.3 ± 0.8*</td>
<td>88.6 ± 2.7</td>
<td>3.1 ± 0.5*</td>
<td>4.0 ± 0.8*</td>
<td>73.6 ± 2.5*</td>
<td>66.5 ± 6.9</td>
<td>4.8 ± 0.4</td>
<td>5.7 ± 0.6</td>
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<tr>
<td>−40 mmHg</td>
<td>0.4 ± 0.8*</td>
<td>85.5 ± 2.2*</td>
<td>2.5 ± 0.5*</td>
<td>2.9 ± 0.6*</td>
<td>74.5 ± 3.0*</td>
<td>63.4 ± 6.4</td>
<td>4.6 ± 0.4</td>
<td>5.6 ± 0.5</td>
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<tr>
<td>−60 mmHg</td>
<td>0.1 ± 0.7*</td>
<td>82.6 ± 3.2*</td>
<td>2.1 ± 0.3*</td>
<td>2.6 ± 0.4*</td>
<td>76.3 ± 3.8*</td>
<td>67.5 ± 8.7</td>
<td>4.9 ± 0.5</td>
<td>6.0 ± 0.7</td>
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<tr>
<td>−75 mmHg</td>
<td>0.8 ± 0.5*</td>
<td>86.1 ± 2.9*</td>
<td>1.6 ± 0.3*</td>
<td>1.9 ± 0.4*</td>
<td>82.8 ± 3.3*</td>
<td>58.2 ± 6.8</td>
<td>4.6 ± 0.4</td>
<td>5.4 ± 0.6</td>
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<tr>
<td>−90 mmHg</td>
<td>1.2 ± 0.6*</td>
<td>87.0 ± 3.2</td>
<td>1.4 ± 0.4*</td>
<td>1.7 ± 0.5*</td>
<td>87.6 ± 4.3*</td>
<td>55.2 ± 6.8</td>
<td>4.5 ± 0.4</td>
<td>5.3 ± 0.7</td>
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<tr>
<td>Heat stress</td>
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<tr>
<td>Control</td>
<td>6.1 ± 0.6†</td>
<td>80.2 ± 2.2†</td>
<td>14.2 ± 1.3†</td>
<td>17.7 ± 1.5†</td>
<td>84.6 ± 3.5†</td>
<td>92.0 ± 8.2</td>
<td>7.6 ± 0.7</td>
<td>10.3 ± 1.0†</td>
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<tr>
<td>LBNP</td>
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<tr>
<td>−10 mmHg</td>
<td>4.5 ± 0.8*</td>
<td>78.3 ± 2.1</td>
<td>13.3 ± 1.0*</td>
<td>17.0 ± 1.2</td>
<td>87.5 ± 3.1</td>
<td>78.4 ± 10.3</td>
<td>6.7 ± 0.7</td>
<td>9.1 ± 0.9</td>
</tr>
<tr>
<td>−20 mmHg</td>
<td>2.9 ± 0.7*</td>
<td>77.1 ± 2.0</td>
<td>10.5 ± 1.2*</td>
<td>13.7 ± 1.7*</td>
<td>89.7 ± 3.7*</td>
<td>73.0 ± 7.6</td>
<td>6.4 ± 0.5</td>
<td>8.7 ± 0.8</td>
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<td>−30 mmHg</td>
<td>2.0 ± 0.8*</td>
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<td>13.5 ± 1.5*</td>
<td>98.2 ± 2.2*</td>
<td>64.0 ± 7.0</td>
<td>6.2 ± 0.6</td>
<td>8.5 ± 0.9</td>
</tr>
<tr>
<td>−40 mmHg</td>
<td>0.6 ± 0.6*</td>
<td>75.4 ± 3.8*</td>
<td>7.6 ± 1.3*</td>
<td>9.7 ± 1.5*</td>
<td>95.6 ± 3.9*</td>
<td>65.1 ± 6.4</td>
<td>6.1 ± 0.5</td>
<td>8.2 ± 0.7</td>
</tr>
<tr>
<td>−60 mmHg</td>
<td>−0.4 ± 0.8*</td>
<td>79.0 ± 1.6</td>
<td>6.3 ± 1.0*</td>
<td>8.0 ± 1.3*</td>
<td>105.7 ± 3.2*</td>
<td>53.6 ± 5.8</td>
<td>5.5 ± 0.5</td>
<td>7.0 ± 0.6</td>
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</tbody>
</table>

Values are means ± SE. LBNP, lower body negative pressure. *Different from control, P < 0.05. †Different from normothermic control, P < 0.05.

Central Hemodynamic Response to LBNP

There was a graded reduction in CVP with each level of LBNP in both the normothermic and heat stress conditions (Table 1). Despite the lower resting CVP during heat stress, CVP at any given level of LBNP was similar in thermoneutral and heat stress conditions. Presyncopal symptoms occurred in only one subject during the last 30 s of −40 mmHg LBNP during heat stress. Data from this trial were not used in any analysis.

CO was consistently higher during passive heating at all levels of CVP (Table 1). However, the slope of the linear relationship between CVP and cardiac SV (Fig. 1) was similar in thermoneutral and passive heating, indicating that the CVP-SV relationship of the heart was not significantly influenced by the increase in body core temperature.

Forearm Blood Flow Response to LBNP

During LBNP there was a linear relationship between the reduction in CVP and the decrease in FVC (Fig. 2). Heat stress increased the slope of this relationship from 0.46 ± 0.10 to 1.57 ± 0.30 ml·100 ml⁻¹ tissue·min⁻¹·100 mmHg⁻¹ per mmHg CVP (P < 0.05). FVC was always greater during heat stress than during thermoneural conditions at all levels of CVP (P < 0.05). The linear relationship between systemic vascular conductance and CVP was also shifted upward, but the slope was not significantly different between thermoneural and passive heating, averaging 0.30 ± 0.05 and 0.48 ± 0.08 l·min⁻¹·100 mmHg⁻¹ per mmHg CVP, respectively (Fig. 2).

Skin Blood Flow Response to LBNP

We observed significant heterogeneity in the CVC response to LBNP (Fig. 3). At thermoneural conditions, application of −60 mmHg LBNP produced a decrease in CVC (≥10%) in only 25% of the subjects. During −75 and −90 mmHg LBNP, 50 and 65% of the subjects showed a decrease in CVC, respectively. During heat stress, application of −40 and −60 mmHg LBNP produced a decrease in CVC in 43 and 57% of the subjects, respectively. At beryllium-treated skin sites, LBNP was ineffective in reducing CVC under thermoneural or heat stress conditions. In addition, LBNP elicited significant vasodilation at the beryllium-treated skin site in three subjects. The group data are presented in Fig. 4, illustrating the relationship be-

![Fig. 1. Cardiac stroke volume as a function of central venous pressure during lower body negative pressure at thermoneutral (0, −10, −20, −30, −40, −60, −75, and −90 mmHg lower body negative pressure) and heat stress conditions (0, −10, −20, −30, −40, and −60 mmHg lower body negative pressure). Values are means ± SE.](http://jap.physiology.org/DownloadedFrom/10220.33.6)
between CVC and CVP during LBNP under thermoneutral and heat stress conditions.

Application of LBNP did not significantly influence mean skin temperature in either thermoneutral or heat stress conditions. For example, mean skin temperature averaged 35.2 ± 0.1°C before and 35.1 ± 0.2°C during −60 mmHg LBNP in thermoneutral conditions and 35.7 ± 0.1°C before and 35.2 ± 0.2°C during −60 mmHg LBNP in heat stress (P > 0.05).

DISCUSSION

There are two major results of this study. First, the relationship between changes in FVC and CVP remains linear over a wide range of LBNP. This linear relationship is shifted to a higher FVC, and the slope is increased by elevations in body core temperature. These data illustrate the integration of thermoregulatory and cardiovascular reflexes, presumably at some
site within the central nervous system. Second, laser-Doppler velocimetry consistently detected changes in CVC during thermal stimuli but failed to identify consistent vasoconstrictor responses to orthostatic stress.

We used selective body core heating to study the interaction between thermal and baroreflexes. This experimental approach was chosen to eliminate any possible influence of high skin temperature, either local or whole body, on vascular responses in the skin (17, 21). Oberle et al. (17) showed that the cutaneous vasomotor response in acral skin to painful intraneural stimulation or arousal was dependent on thermal status. Specifically, intraneural stimulation caused vasodilation when foot skin temperature was <0°C but produced vasoconstriction when the skin temperature was >33°C. These authors concluded that skin vasomotor responses to various stimuli are modulated by skin temperature and that mean skin temperature was more important than local skin temperature. In addition, warming a large portion of the skin surface to a high temperature will modify the overall hemodynamic response to venous pooling during LBNP and thereby alter the physiological signal responsible for eliciting a baroreflex response (18, 19). The data in Fig. 1 indicate that our heating protocol reduced resting CVP but did not alter the linear relationship between CVP and cardiac SV during LBNP. However, the greater changes in FVC during heat stress resulted in relatively smaller changes in CVP.

The upward shift and increase in slope of the FVC-CVP relationship (Fig. 2) provide evidence that the baroreflex control of peripheral blood flow (mostly skin) is modulated with regard to thermoregulatory demands. It is generally assumed that the quantitative contribution of muscle blood flow to the changes in FVC is not affected by thermal stress (3, 4). In that respect, our results are similar to earlier reports by Crossley et al. (2) and Johnsen et al. (8), who found greater reductions in FVC during bouts of LBNP of −50 or −70 mmHg, respectively, with increasing thermal stress. The linearity of the CVP-FVC relationship over the entire range of nonhypotensive and hypotensive LBNP suggests a single response “element.” One interpretation of these data is that the cardiopulmonary baroreceptors represent the primary response element with little additional contribution due to arterial baroreceptor unloading. This interpretation is supported by Crandall et al. (1), who found no change in the CVC in response to application of pulsatile carotid pressure. The increase in slope of the FVC-CVP relationship might suggest that heat stress increased the sensitivity of this baroreflex. We chose an alternative analysis of these data and evaluated the changes in FVC as a function of the level of LBNP. In this analysis, it is assumed that with increasing levels of LBNP the change in FVC would reach some asymptote representing the maximal vasoconstrictor response. This analysis is shown graphically in Fig. 5 as a plot of the change in FVC as a hyperbolic function of LBNP that saturates maximal vasoconstrictor capacity (ΔFVCmax) at some high level of LBNP. Curve fitting the data by using the following equation

$$\Delta FVC = \frac{\Delta FVC_{max} \cdot LBNP}{(K_m + LBNP)}$$

allows estimation of ΔFVCmax and the Km or the level of LBNP that produces 50% of ΔFVCmax. A comparison of the mean responses indicates that ΔFVCmax increased from 5.2 ml·100 ml−1·min−1·100 mmHg−1 in thermoneutral conditions to 12.8 ml·100 ml−1·min−1·100 mmHg−1 during heat stress. One interpretation of this analysis is that the capacity to respond to LBNP increased with heat stress. This conclusion is consistent with the observations of Johnsen et al. (7, 8). The Km was unchanged by thermal stress, averaging −27 and −24 mmHg LBNP, respectively. These data suggest that the responsiveness of vascular control of FVC during LBNP, presumably by baroreceptors, is unchanged by a mild elevation of body core temperature.

Our laser-Doppler measurements demonstrate significant changes in CVC to thermal stimuli, i.e., a reduction by ~25% in the untreated skin site in response to cold stress and a 300–400% increase in response to heat stress. (Fig. 4) These findings are consistent with the reports by Kellogg et al. (11) and
Crandall et al. (1). Interestingly, during heat stress, CVC was lower in the bretylium-treated than in the untreated skin site. A diminished vasodilator response in the skin to thermal stress has also been observed in studies using standard plethysmographic measurements of forearm blood flow after sympathectomy (5) and cutaneous nerve blockade (4) and in laser-Doppler studies after sinoaortic denervation (20). A similar trend was reported in two studies by Kellogg et al. (10, 11), in which thermal stress increased CVC by 419 ± 66 and 361 ± 57% in treated skin sites vs. 517 ± 90 and 497 ± 82% in untreated skin sites, respectively. Ryan et al. (20) speculated that the loss of baroreceptor input to the central nervous system associated with sinoaortic denervation may limit maximal thermoregulatory responses at some “central” site by a yet-undefined mechanism. However, the observation that both cutaneous nerve blockade and local bretylium iontophoresis reduce maximal cutaneous vasodilatation is in conflict with the view that the cutaneous vasodilator system is exclusively controlled by nonadrenergic mechanism.

In contrast to the thermal stimuli, nonhypotensive or hypotensive levels of LBNP did not evoke significant reductions in CVC. There were few subjects (n = 3) who showed consistent vasoconstrictor responses to LBNP. Even in these subjects, clear reductions in CVC were only evident during application of LBNP greater than −40 mmHg. More surprising was the one subject who showed substantial vasodilation during LBNP. It is difficult to clearly interpret our laser-Doppler findings in view of the plethysmographic data. One possibility is that there is significant spatial heterogeneity in the skin blood flow responses during LBNP. This conclusion is supported by a study from our laboratory (14) that conducted topographical perfusion mapping of a 6.25-cm² skin area by laser-Doppler scanning. This study found uniform changes in CVC in ~90% of the skin during cold stress and heat stress. In contrast, only 47% of the skin area showed a reduction in CVC during −40 mmHg LBNP, 28% was unaffected, and 26% showed an increase in CVC. One possible interpretation is that the overall and hemodynamically relevant blood flow response to LBNP is more accurately reflected by the strain-gauge technique. Johnson et al. (9) have emphasized the great region-to-region and study-to-study variability of the laser-Doppler measurements and concluded that the region under observation may be too small to have uniform responses or uniform numbers of perfused capillaries from site to site.

Two earlier studies have also found no changes in CVC during nonhypotensive LBNP (1, 25). However, Crandall et al. (1), Kellogg et al. (11), and Tripathi and Nadel (24) have reported consistent reductions in CVC in response to −30 or −40 mmHg LBNP, respectively. These data are in conflict with our laser-Doppler data and with the work of Vissing et al. (26). The latter found no changes in CVC or skin sympathetic nerve activity during 20 min of −50 mmHg LBNP. The reason for these inconsistencies is unclear. Possible explanations may be the nonuniform nature of skin blood flow responses to baroreceptor unloading and differences in the experimental protocol with regard to the application of heat stress, i.e., whole body skin heating vs. body core heating. For example, skin temperatures in the studies by Kellogg et al. (10, 11) were 38–39°C, whereas our protocol produced skin temperatures of 35.7°C. Taylor et al. (23) have shown that 2°C differences in local skin temperature significantly alter reflex cutaneous vasoconstriction in response to mild exercise and concluded that the greatest changes may be observed at local skin temperatures of ∼39°C. Hence, the >2.3°C difference in mean skin temperature may impact the peripheral pooling associated with LBNP and the reflex cardiovascular responses, including those responses in the cutaneous vasculature. In the present study, mean skin temperature was unchanged during LBNP, and little changes in CVC were observed. It is possible that changes in mean skin temperature contribute to the magnitude of the CVC response to LBNP, as suggested by Vissing et al. (25). However, an alternative explanation is that poor resolution of the baroreflex control of CVC is due to a combination of individual differences in baroreflex control of CVC (Fig. 5) and spatial heterogeneity associated with sampling skin blood flow with laser-Doppler flow probes (15). Finally, our plethysmographic measurements argue against the conclusion of Vissing et al. (26) that the cutaneous circulation is not under baroreceptor control.

The skin blood flow response to LBNP at skin sites treated with bretylium tosylate was also absent. One possible explanation would be differences in the bretylium iontophoresis protocols. Kellogg et al. (10) used a greater current density (400 µA/cm²) for only 10 min, equivalent to 4,000 µA·min·cm⁻², compared with 4,800 µA·min·cm⁻² produced by our protocol. There were moderate differences in the sizes of the iontophoresis chambers (0.64 vs. 3.1 cm²), and Kellogg et al. used propylene glycol as a delivery solution, whereas we used pure water as solvent. However, both methods produced effective adrenergic blockade on the basis of
the abolition of the reflex vasoconstriction during skin cooling. Because pure water does not conduct current, the control sites in our study were not actually exposed to current without drug. Grossmann et al. (6) have shown that iontophoresis may cause a current-related hyperemia independent of the action of the administered agent. In the present study, there was no difference in baseline CVC between the sites under normothermic conditions, and the heat-induced CVC changes were greater in the untreated site. Hence, we do not believe that our bretylum iontophoresis protocol is an important confounding factor.

Another interesting question arising from our measurements is the putative mechanism by which CVC increased during severe LBNP. In theory, this could be a passive phenomenon if there is a reduction in arteriolar constriction in the vicinity. Alternatively, a vasodilator system may have been activated in association with presyncopal or emotional stress. Because CVC increases during LBNP were also observed in the heated state, when all vasoconstrictor tone is presumably released, active vasodilatation appears to be the most probable explanation. Such responses, when occurring more uniformly, may contribute importantly to orthostatic intolerance.

In summary, the present study suggests that there is an important central integration of thermoregulatory and baroreflexes directed to the cutaneous circulation. In addition, it is likely this interaction is mediated primarily by the cardiopulmonary baroreceptors. Our laser-Doppler data indicate significant regional heterogeneity of the skin blood flow responses to orthostatic stress. This latter observation, although intuitively puzzling, may be viewed as indirect evidence for the existence of a sympathetic active vasodilator system. A vasodilator component of skin sympathetic nerve activity (22) has been identified. Preliminary data from our laboratory (16) showed that this vasodilator component of skin sympathetic nerve activity was present at skin temperatures of 34°C. These observations, in combination with our present data, support the hypothesis that vasomotor response of the cutaneous vasculature to increased sympathetic nerve activity reflect a net balance between dilating and constricting effects. In addition, this net balance appears to be modulated by thermal status acting either centrally (Fig. 2) and/or locally (17).

We thank Dr. John Fahey and John Stefan for technical assistance and the volunteer subjects for time and cooperation.

This work was supported by National Heart, Lung, and Blood Institute Grant HL-39818.

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Received 19 June 1996; accepted in final form 5 January 2000.

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