Mechanisms of cutaneous vasoconstriction during orthostasis in heat stressed individuals.

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Introduction
Cutaneous vasoconstriction during orthostatic stress contributes to the maintenance of blood pressure. During pronounced heat stress, up to ~50% of cardiac output is distributed to the cutaneous circulation (1,2). Therefore the control of cutaneous vascular conductance (CVC) is an important factor during combined orthostatic and heat stresses. The cutaneous circulation is controlled by two neural systems: a sympathetic adrenergic vasoconstrictor system and a separate sympathetic non-adrenergic active vasodilator system (3). The active vasodilator system accounts for 85 to 95% of the overall cutaneous vasodilator response during heat stress (4). During orthostasis of a heat stressed individual, reductions in CVC could occur by engagement of the vasoconstrictor system and/or by withdrawal of the active vasodilator system. Previous studies confirmed the contribution of a withdrawal of the active vasodilator system leading to this cutaneous vasoconstriction (5,6). However, the contribution of enhanced vasoconstrictor activity to this response remains unknown. The purpose of this study was to identify whether orthostatic stress is capable of increasing cutaneous vasoconstrictor activity in heat stressed individuals.

Methods
Thirteen healthy subjects participated in this study. Botulinum toxin A (BOTOX) was administered to the dorsal forearm by intradermal injection at least 3 days prior to experimentation. On the experimental day, each subject was dressed in a tube-lined water perfusion suit that permitted the control of skin temperature, and then placed in a lower body negative pressure (LBNP) device that was sealed at the iliac crest. Two microdialysis probes were placed in the intradermal space of the dorsal aspect of one forearm. One probe was placed in the BOTOX pretreated area and the other was placed in an adjacent untreated control area. Probes were perfused with Ringer’s solution at a rate of 2 μl min⁻¹ for approximately 90-120 min after probe placement, allowing the hyperemic response associated with membrane placement to subside. Vasoconstrictor responsiveness was assessed by performing a 3 min cold stress in which 5°C water was perfused through the suit. Once skin blood flow returned to baseline (34°C water circulation), a heat stress ensued by perfusing 46°C water through the suit. After confirmation of cutaneous vasodilation at the control site but not at the BOTOX site, either the β agonist isoproterenol (ISO) or the nitric oxide donor sodium nitroprusside (SNP) was infused through the microdialysis membrane at the BOTOX site to increase skin blood flow. The concentrations of isoproterenol (8.1x10⁻⁶ to 8.1x10⁻⁵ M) and SNP (6.4x10⁻⁵ to 8.4x10⁻⁵ M) were administered until skin blood flow at the BOTOX site was similar relative to the control site. After baseline measurements, 30 or 40 mmHg of LBNP was applied for 3 min or until the onset of pre-syncope symptoms. After the end of the LBNP test, 50mM of SNP was infused through both microdialysis membranes to cause maximum vasodilation. Cutaneous vascular conductance (CVC) was calculated from the ratio of skin blood flow to mean arterial pressure and the data were normalized against maximal vasodilation (%/max).

Results & Discussion
Cold stress decreased CVC at both sites (control: 13.3 ± 4.9 to 7.0 ± 3.5%/max, BOTOX: 13.6 ± 5.7 to 9.6 ± 4.4%/max, both P<0.01). The magnitude of the reduction in CVC during cold stress was not different between sites, suggesting that BOTOX did not affect the vasoconstrictor system. Whole-body heating elevated internal temperature and increased skin blood flow at the control site for both protocols. In contrast, CVC at the BOTOX site did not change as a result of whole-body heating. Prior to LBNP, CVC was not different between the control and BOTOX+drug sites for either protocol (ISO: 60.7 ± 10.4 vs. 55.4 ± 13.4%/max, SNP: 56.7 ± 9.2 vs. 44.3 ± 14.3%/max, both P>0.05). The application of LBNP decreased CVC at the control and the BOTOX+ISO sites, but the magnitude of the reduction in CVC was significantly greater at the control site relative to the BOTOX site (-8.8 ± 5.6% vs. -15.3 ± 4.6%/max; P>0.05). In contrast, CVC at the BOTOX+SNP site did not change (+1.1 ± 5.0%/max) during LBNP. These results suggest that orthostatic stress activates the cutaneous vasoconstrictor system in heat stressed subjects, but substance(s) released from active vasodilator system may inhibit cutaneous vasoconstrictor responsiveness.

References