

Evidence of a myogenic response in vasomotor control of forearm and palm cutaneous microcirculations

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Durand, S., R. Zhang, J. Cui, T. E. Wilson, and C. G. Crandall. Evidence of a myogenic response in vasomotor control of forearm and palm cutaneous microcirculations. *J Appl Physiol* 97: 535–539, 2004. First published April 16, 2004; 10.1152/jappphysiol.01299.2003.— Previous investigations of autoregulatory mechanisms in the control of skin blood flow suffer from the possibility of interfering effects of the autonomic nervous system. To address this question, in 11 subjects cutaneous vascular responses were measured during acute changes in perfusion pressure (using Valsalva maneuver; VM) before and after ganglionic blockade via systemic trimethaphan infusion. Cutaneous vascular conductance at baseline (CVC_{base}) and during the last 5 s of the VM (CVC_{VM}) were measured from forearm (nonglabrous) and palm (glabrous) skin. During the VM without ganglionic blockade, compared with CVC_{base} , CVC_{VM} decreased significantly at the palm [0.79 ± 0.17 to 0.55 ± 0.17 arbitrary units (AU)/mmHg; $P = 0.002$] but was unchanged at the forearm (0.13 ± 0.02 to 0.16 ± 0.02 AU/mmHg; $P = 0.50$). After ganglionic blockade, VM induced pronounced decreases in perfusion pressure, which resulted in significant increases in CVC_{VM} at both forearm (0.19 ± 0.03 to 0.31 ± 0.07 AU/mmHg; $P = 0.008$) and palm (1.84 ± 0.29 to 2.76 ± 0.63 AU/mmHg; $P = 0.003$) sites. These results suggest that, devoid of autonomic control, both glabrous and nonglabrous skin are capable of exhibiting vasomotor autoregulation during pronounced reductions in perfusion pressure.

autoregulation; skin blood flow; Valsalva maneuver

CUTANEOUS TISSUE HAS RELATIVELY low metabolic requirements, and control of skin blood flow is primarily influenced by thermal factors (e.g., local and internal temperatures). Skin blood flow can also be modulated by nonneurally mediated events, one of which may be vascular cutaneous autoregulation. Vascular autoregulation serves to maintain blood flow and nutrient supply when perfusion pressure is altered. In addition, autoregulatory responses attenuate large changes in capillary pressure that otherwise would occur during changes in perfusion pressure (15).

Cutaneous blood flow during normothermic conditions is in excess of that required to provide for its metabolic demand. Given this, the requirement to autoregulate blood flow through this vascular bed during relatively small changes in perfusion pressure would be less critical relative to other vascular beds. Such a response is likely advantageous given that precise autoregulation of cutaneous vasculature would oppose thermally induced cutaneous vasoconstriction and vasodilation, which are necessary to maintain temperature homeostasis (21).

The venoarteriolar response is an example of a vascular autoregulatory mechanism that has been identified and widely

investigated in human skin (3, 7, 9, 13, 23). However, the stimulus for this response is a change in venous pressure regardless of whether perfusion pressure changes or remains constant. This response also requires an intact local neural network (3, 7, 10, 13, 23), which is in contrast to traditional myogenic vascular autoregulation. Thus findings pertaining to the cutaneous venoarteriolar response shed little insight regarding whether cutaneous tissue is capable of modulating vascular tone specifically due to changes in perfusion pressure. Given this, the purpose of the present study was to test the hypothesis that the cutaneous vasculature is capable of exhibiting myogenic responses during acute reductions in perfusion pressure. To accomplish this objective, without the possible confounding effects of sympathetic control of skin blood flow, cutaneous vascular conductance (CVC) was assessed during changes in perfusion pressure induced by the Valsalva maneuver (VM) after systemic administration of a ganglionic-blocking agent. In addition, because glabrous skin is rich in arteriovenous anastomoses, which are reported to have few intrinsic myogenic properties (4, 5), identification of cutaneous myogenic autoregulation was assessed in both glabrous and nonglabrous skin.

METHODS

Subjects. Eleven subjects (8 men and 3 women) participated in this study. They were 29.6 ± 2.1 yr of age and were of normal height (172.4 ± 2.9 cm) and weight (69.8 ± 3.0 kg). Subjects were nonsmokers, were not taking any medications, and did not have any cardiopulmonary, neurological, or metabolic diseases. Each subject signed an informed consent that was approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas.

Protocol. Procedures were performed with the subject in the supine position in a quiet temperature-controlled room (24°C). Forearm (nonglabrous) and palm (glabrous) cutaneous blood flows were continuously measured via laser-Doppler flowmetry (Perimed, North Rayalton, OH) at a frequency of 100 Hz. Heart rate was obtained from an electrocardiogram (SpaceLabs, Redmond, WA) with the signal interfaced with a cardiometer (CWE, Ardmore, PA). Arterial blood pressure was monitored from a catheter placed in the radial artery ($n = 3$) or from a finger via a Finapres (Ohmeda, Louisville, CO; $n = 8$). Mean arterial blood pressure was obtained from the integration of the pressure signal. For the Finapres trials, the finger was kept at heart level throughout. For the arterial catheter trials, the pressure transducer was zeroed at a level equivalent to 5 cm caudal to the sternum. Because no significant difference was observed between these two methods, arterial blood pressure data were pooled for statistical analysis. Heart rate, arterial blood pressure, and forearm and

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palm cutaneous blood flows were monitored throughout the experimental protocol. A venous catheter was placed in an antecubital vein for the infusion of the ganglionic blocking agent (trimethaphan camsylate, Cambridge Laboratories, UK).

The protocol was initiated with the subject performing VMs under control (i.e., nonganglionic-blocked) conditions. A mouthpiece was put into the subject's mouth, which was connected to an analog manometer to monitor changes in intrathoracic pressure. After 1 min of spontaneous breathing, at the end of a normal inspiration, the subject blew against an obstructed airway and maintained a pressure of 30 mmHg for 15 s.

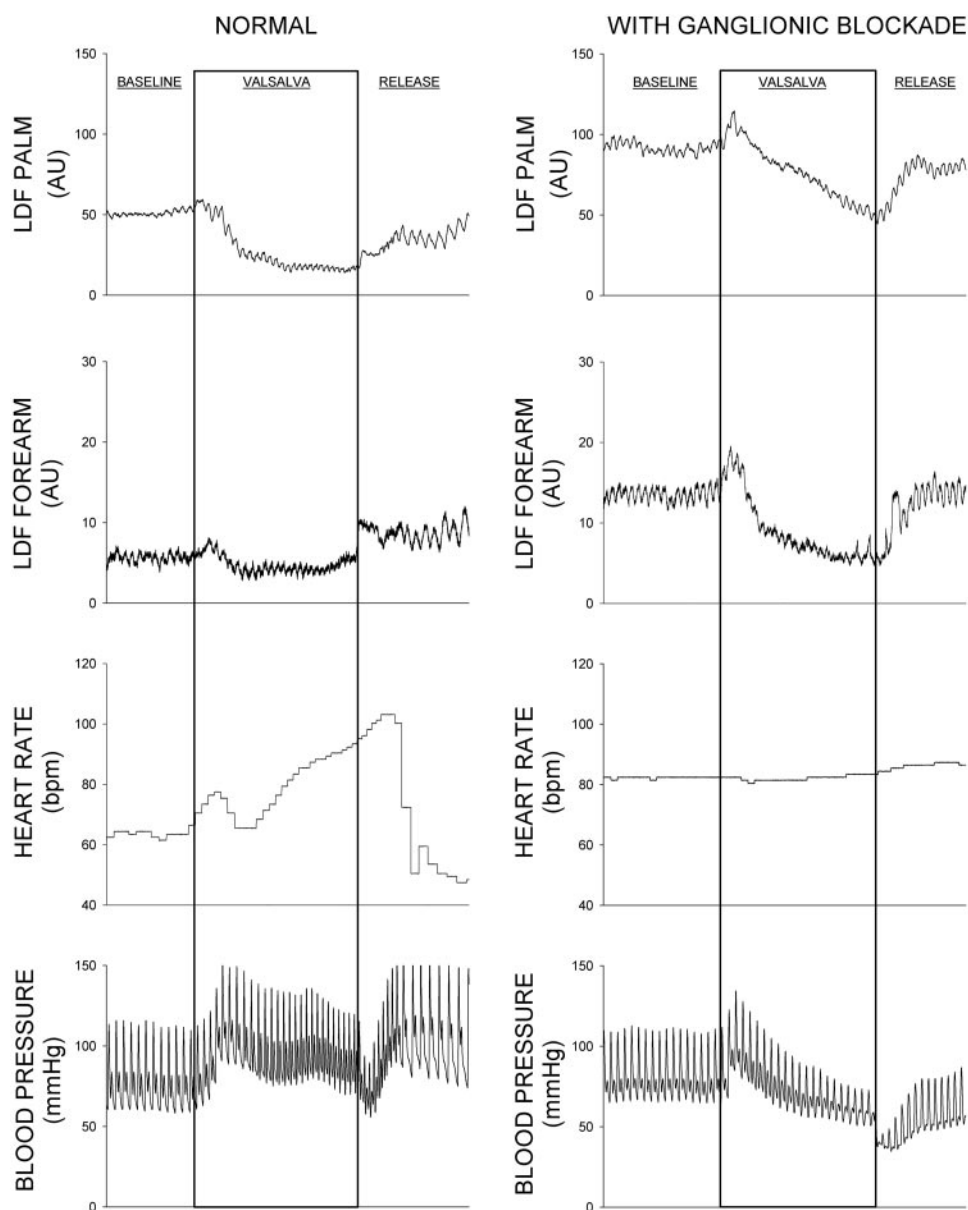
After completion of baseline VMs, administration of trimethaphan began at a dose of 3 mg/min. Three minutes after the infusion, a VM was repeated to evaluate heart rate response during this maneuver. The infusion rate was increased incrementally by 1 mg/min until the heart rate response during the VM was either completely or significantly attenuated (see Fig. 1). The absence and/or attenuation of the heart rate response demonstrated the efficacy of ganglionic blockade (19, 24, 25). A minimum of 2 min elapsed between successive VMs. The final dose of trimethaphan varied between subjects with 6–7

mg/min being used for most subjects. Data during the VM with the most complete ganglionic blockade (i.e., highest dose of trimethaphan) were compared with responses during nonganglionic-blocked VM.

Skin blood flow was measured during a 30-s interval before each VM (baseline) and the last 5 s of the VM; the latter corresponds to the late phase II (phase IIb) of the VM (17, 19, 22). Data during this phase of the VM were analyzed because of sustained decreases in arterial blood pressure after ganglionic blockade (24). Cutaneous vascular conductance at baseline (CVC_{base}) was calculated from the ratio of skin blood flow and mean arterial blood pressure. During phase IIb of the VM, because increases in intrathoracic pressure result in similar increases in venous pressure (6), cutaneous perfusion pressure under these conditions was estimated as mean arterial pressure minus intrathoracic pressure (30 mmHg). Thus, at this phase of the VM, cutaneous vascular conductance (CVC_{VM}) was calculated from the ratio of skin blood flow to estimated cutaneous perfusion pressure.

A subset of subjects ($n = 3$) performed VM under control conditions (i.e., nonganglionic blocked) while cutaneous vascular responses were assessed from areas of skin (palm or forearm) locally anesthe-

Fig. 1. Typical cutaneous vascular, blood pressure, and heart rate responses to a control Valsalva maneuver (VM; *left*) and ganglionic-blocked VM (*right*). Rectangular box indicates the VM. Note the increase in heart rate before VM after ganglion blockade and the absence of a significant change in heart rate during the subsequent VM. The absence of a heart rate response during the ganglionic-blocked VM demonstrates the efficacy of blockade. LDF Palm, laser-Doppler-derived palm skin blood flow; LDF Forearm, LDF-derived skin blood flow; AU, arbitrary units; bpm, beats/min.



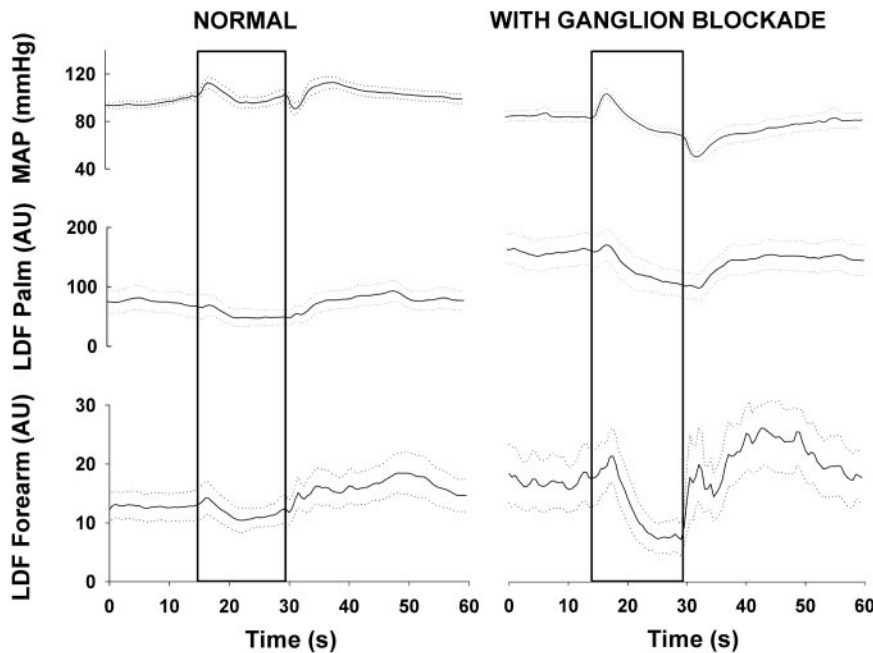


Fig. 2. Mean arterial blood pressure (MAP) and LDF Palm and LDF Forearm before, during, and after the Valsalva maneuver (rectangular box). Data are presented as means (solid lines) \pm SE (dotted lines). *Left*, unblocked responses; *right*, responses during ganglionic blockade.

tized with intradermal injection of 10% lidocaine (without epinephrine) or topical application of EMLA cream. Lidocaine was preferred to EMLA cream to locally anesthetize skin at the palm because of unsatisfactory anesthesia with EMLA cream on the palmar surface (personal observation). CVC was calculated as described above both at locally blocked sites and adjacent unblocked sites.

Statistical analysis. At each site, CVC and arterial blood pressure were statistically analyzed via a two-way repeated-measures ANOVA with the following main factors: condition (i.e., control vs. blocked) and VM stage (i.e., baseline vs. phase IIb). If a significant interaction was identified, post hoc analyses were performed on paired comparisons (Bonferonni corrected paired *t*-tests). Results are presented as means \pm SE. The level of statistical significance was set at $P \leq 0.05$.

RESULTS

Figure 1 depicts typical heart rate, arterial blood pressure, and cutaneous blood flow responses to a VM with and without sympathetic ganglionic blockade. Mean responses for arterial blood pressure and forearm and palm skin blood flows during both control and ganglionic-blocked VMs are presented in Fig. 2. During the nonganglionic-blocked VM, typical arterial blood pressure responses were observed. For this VM, at the forearm, there was no statistical difference between CVC_{base} [0.13 ± 0.02 arbitrary units (AU)/mmHg] and CVC_{VM} (0.16 ± 0.02 AU/mmHg; $P = 0.50$), whereas palm vascular conductance was significantly reduced during the VM (CVC_{base} : 0.79 ± 0.17 ; CVC_{VM} : 0.55 ± 0.17 AU/mmHg; $P = 0.002$; Fig. 3).

Trimethaphan administration significantly decreased mean arterial blood pressure before the VM (pretrimethaphan: 94.8 ± 3.1 , trimethaphan: 85.1 ± 4.5 mmHg; $P = 0.047$). The typical heart rate response to the VM was abolished (see Fig. 1), demonstrating effective ganglionic blockade. Ganglionic blockade significantly increased palm CVC_{base} (1.84 ± 0.29 AU/mmHg) compared with the control condition (0.79 ± 0.17 AU/mmHg; $P = 0.018$). On the contrary, there was only a tendency for forearm CVC_{base} to be elevated on ganglionic blockade (control: 0.13 ± 0.02 AU/mmHg; ganglionic blocked: 0.19 ± 0.03 AU/mmHg; $P = 0.26$).

During phase IIb of the ganglionic-blocked VM, calculated perfusion pressure was substantially reduced (37.0 ± 3.9 mmHg) compared with this period during the control VM (73.7 ± 4.5 mmHg; $P < 0.001$). During this phase of the ganglionic-blocked VM, both forearm CVC_{VM} (0.19 ± 0.03 to 0.31 ± 0.07 AU/mmHg; $P = 0.008$) and palm CVC_{VM} (1.84 ± 0.29 to 2.76 ± 0.63 AU/mmHg; $P = 0.003$) were significantly elevated compared with baseline (Fig. 3). These findings indicate that, in the absence of neural innervation, both glabrous and nonglabrous cutaneous vascular beds are capable of dilating during pronounced reductions in perfusion pressure. It is interesting to note that, at the forearm, but not in the palm, large increases in CVC occurred on the release of the VM (see Fig. 2).

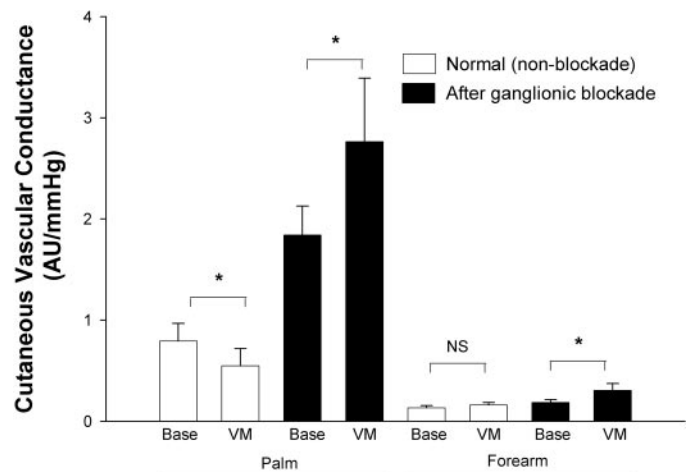


Fig. 3. Palm and forearm cutaneous vascular conductance (means \pm SE) before (Base) and during the last 5 s of the VM. Open bars, control VM; solid bars, ganglionic-blocked VM. Cutaneous perfusion pressure during the VM was determined as MAP minus intrathoracic pressure (30 mmHg). NS, not significantly different between Base and VM conditions. *Significantly different between Base and VM conditions, $P < 0.05$.

In the subset of subjects, local cutaneous blockade at the palm and the forearm was confirmed via absence of tactile sensation. Perfusion pressure responses to the subsequent VM were similar to the control VM depicted in Fig. 1 (*left*). Local anesthetic did not alter CVC responses during this nonganglionic-blocked VM (Table 1).

DISCUSSION

The primary finding of this study is that both glabrous and nonglabrous skin exhibit myogenic responses as evidenced by a significant increase in CVC during pronounced reductions in perfusion pressure. However, the increase in CVC was insufficient to maintain skin blood flow as marked decreases in skin blood flow occurred during the VM (Fig. 2). In contrast, with an intact sympathetic nervous system, the VM reduced palm CVC, whereas, for the forearm, the reduction in blood flow was similar relative to the reduction in perfusion pressure such that forearm CVC was unchanged.

Associated with well-described changes in arterial blood pressure, during the VM, the increase in intrathoracic pressure causes similar increases in venous pressure (6). This increase in venous pressure contributes to the reduction in perfusion pressure during the VM. Given the effects of the VM on reducing perfusion pressure, especially during ganglionic blockade, the VM was used to assess autoregulatory capabilities of the skin. In the unblocked condition, the VM induced significant decreases in palm CVC, whereas no change in forearm CVC was identified. The palm is characterized by its richness in arteriovenous anastomoses (2, 12), which are highly sensitive to vasomotor reflexes because of the high level of sympathetic innervation of these anastomoses. Thus it is possible that differing responses between palm and forearm CVC during the unblocked VM were due to morphological differences, and associated differences in sympathetic innervation, of glabrous vs. nonglabrous skin.

After ganglionic blockade, CVC responded quite differently to the VM. A significant increase in both forearm and palm CVC occurred at the end of the VM. These findings show that, in response to greatly reduced perfusion pressure, cutaneous vascular smooth muscle is capable of autoregulation. A local vasodilator myogenic mechanism appears to be the most likely explanation for the observed increase in CVC during the blocked VM. However, despite cutaneous vasodilation, skin blood flow remained well below baseline during the VM.

Table 1. *Palm and forearm cutaneous vascular conductance during the 30-s period before and at the end of the Valsalva maneuver both with and without local anesthesia*

	Control		With Local Anesthesia	
	CVC _{base}	CVC _{VM}	CVC _{base}	CVC _{VM}
Palm	2.22 ± 0.23	0.86 ± 0.13*	3.54 ± 0.27	3.73 ± 0.32
Forearm	0.13 ± 0.02	0.15 ± 0.02	0.14 ± 0.04	0.10 ± 0.02

Values are means ± SE given in arbitrary units/mmHg. CVC_{base}, cutaneous vascular conductance before the Valsalva maneuver; CVC_{VM}, cutaneous vascular conductance at the end of the Valsalva maneuver. Local forearm anesthesia was performed via topical application of EMLA cream for a minimum of 90 min before the Valsalva maneuver. Palmar anesthesia was accomplished via intradermal injection of 10% lidocaine without epinephrine. *Significant differences between CVC_{base} and CVC_{VM} periods, $P < 0.05$.

Important distinctions exist between the aforementioned myogenic response, relative to the widely studied venoarteriolar response. The venoarteriolar response results in vasoconstriction on increases in venous pressure and vasodilation on reductions in venous pressure. This response has been identified in skin, subcutaneous tissue, and muscle (3, 8, 10, 11, 13, 23). The venoarteriolar response is generally preserved in individuals with a neuronal lesion proximal to the site of measurement (23), but it is absent during application of local anesthesia at the site of blood flow measurement (3, 7, 10, 23). Importantly, this response is independent of perfusion pressure because similar vasoconstrictor responses are observed during limb suspension, when venous pressure is elevated but perfusion pressure is unaffected, relative to venous occlusion in which venous pressure is elevated and perfusion pressure is reduced. In the present study, although venous pressure is elevated, arterial pressure is greatly reduced at the end of the ganglionic-blocked VM, the combination of which results in pronounced reductions in perfusion pressure. It is proposed that this large reduction in perfusion pressure is the primary stimulus leading to cutaneous vasodilation via a myogenic response, despite the elevation in venous pressure, which would otherwise result in cutaneous vasoconstriction. However, it is recognized that the cutaneous vascular response during the ganglionic-blocked VM may result from a combination of vasoconstrictor influences from the venoarteriolar response (secondary to increases in venous pressure) and vasodilator influences (secondary to reductions in perfusion pressure).

Autoregulatory mechanisms, such as myogenic vascular responses, are thought to be primarily activated within a specific range of perfusion pressures (16). In the present study, sympathetic ganglion blockade decreased baseline blood pressure by ~10 mmHg. This reduction in baseline blood pressure, coupled with pronounced decreases in blood pressure during the ganglionic-blocked VM, resulted in pronounced reductions in perfusion pressure (see Fig. 2). To identify whether this large reduction in perfusion pressure contributed to the outcome of the cutaneous vascular responses, in a subset of subjects neural activity in palm and forearm skin was locally blocked via intradermal injection of 10% lidocaine or application of EMLA cream, respectively. Despite this local neuronal blockade, no change in either forearm or palm CVC was observed during the VM (Table 1). These findings are in contrast to an increase in CVC at the end of ganglionic-blocked VM, when perfusion pressure was substantially lower, and a reduction in palm CVC during the control VM. Thus it is proposed that, to observe a myogenic response in palm and forearm skin, perfusion pressure must be substantially reduced, whereas small reductions in perfusion pressure are inadequate to evoke such a response. This response is not surprising because, even during normothermic conditions, skin blood flow is greater than that necessary to meet the relatively low metabolic demands of the skin. Consequently, it may be that cutaneous autoregulation only occurs when perfusion pressure is greatly reduced.

Limitations of the study design. The primary indicator of a successful blockade after trimethaphan administration was an absence of a heart rate response to a VM. The premise was that, if neural activity to the heart was blocked, then neural activity to the vasculature was also blocked. However, this latter point could not be directly validated. Thus we cannot conclusively indicate that all neural activity to the skin was abolished by

ganglionic blockade. However, three observations are consistent with a substantial vascular blockade after trimethaphan administration. First, palm CVC was significantly elevated after ganglionic blockade. Second, baseline blood pressure was significantly reduced after trimethaphan administration. Finally, the pattern of change in blood pressure during the VM was vastly different between control and ganglionic-blocked trials. Together, these observations strongly suggest either complete or substantial blockade of neural control of the vasculature.

Evaluation of ganglionic blockade by trimethaphan necessitated repeated VM to confirm a successful blockade. Thus, in addition to the control VMs, each subject performed three to five additional VM during trimethaphan administration. Although doubtful, we cannot exclude the possibility that repeated VM may have affected cutaneous vascular responses reported during ganglionic blockade independent of that blockade. However, such a mechanism is unlikely given the pronounced difference in arterial blood pressure response during the ganglionic-blocked VM (see Fig. 1) and associated differences in CVC responses between control and ganglionic-blocked VMs.

Skin vascular conductance was indexed by using laser-Doppler flowmetry. Although this technique does not provide absolute skin blood flow values, it accurately and continuously tracks changes in skin blood flow (14) without being influenced by muscle blood flow (20). This technique has been routinely used to assess skin blood flow responses to a variety of perturbations that induced rapid changes in perfusion pressure, including VM (1, 18). Thus we are confident that CVC provides an accurate index of cutaneous vasomotor tone during the VM.

Conclusion. Autoregulatory mechanisms contribute in the maintenance of blood flow. However, the contribution of autoregulation in controlling blood flow varies between vital organs such as brain or myocardium relative to the skin (16). In the present study, evidence of cutaneous autoregulation occurred only under conditions of combined neural blockade and substantial reductions in perfusion pressure (i.e., ganglionic-blocked VM), whereas local neural blockade with relatively minor reductions in perfusion pressure (i.e., local anesthetic blockade VM) did not reveal cutaneous autoregulation. Given that large reductions in perfusion pressure were necessary to observe a myogenic response, it is doubtful that cutaneous autoregulation significantly modulates skin blood flow in healthy individuals. On the other hand, it is possible that cutaneous autoregulation contributes to short-term control of cutaneous blood flow in individuals with diseases such as autonomic failure when pronounced reduction in perfusion pressure may occur during a variety of perturbations.

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DISCLOSURES

This project was a component of a larger project of which data have been previously presented (24, 25).

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