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Vasoconstriction during venous congestion: effects of venoarteriolar response, myogenic reflexes, and hemodynamics of changing perfusion pressure

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Okazaki, Kazunobu, Qi Fu, Emily R. Martini, Robin Shook, Colin Conner, Rong Zhang, Craig G. Crandall, and Benjamin D. Levine. Vasoconstriction during venous congestion: effects of venoarteriolar response, myogenic reflexes, and hemodynamics of changing perfusion pressure. *Am J Physiol Regul Integr Comp Physiol* 289: R1354–R1359, 2005. First published July 7, 2005; doi:10.1152/ajpregu.00804.2004.—We dissected the relative contribution of arteriovenous hemodynamics, the venoarteriolar response (VAR), and the myogenic reflex toward a decrease in local blood flow induced by venous congestion. Skin blood flow (SkBF) was measured in 12 supine subjects via laser-Doppler flowmetry 1) over areas of forearm and calf skin, in which the VAR was blocked by using eutectic mixture of local anesthetics (EMLA sites) and 2) over the contralateral forearm or calf skin (control sites), using two different techniques: limb dependency of 23–37 cm below the heart and cuff inflation to 40 mmHg. During limb dependency, SkBF decreased at the control sites, whereas it remained unchanged at the EMLA sites. In contrast, during cuff inflation, SkBF decreased at the control sites and also decreased at the EMLA sites. The percent change in SkBF from baseline was greater during cuff inflation than limb dependency at both the control sites and the EMLA sites. Estimated skin vascular resistance remained unchanged at the EMLA sites during cuff inflation, as well as limb dependency. Thus the decrease in SkBF during venous congestion with cuff inflation is not solely due to the cutaneous VAR but also to a reduction in local perfusion pressure. The VAR is therefore most specifically quantified by venous congestion induced by limb dependency, rather than cuff inflation. Finally, from both techniques, we calculated that during venous congestion induced by limb dependency (calf), ~45% of the nonbaroreflex vasoconstriction is induced by the VAR and ~55% by the myogenic reflex.

local circulatory control; axon reflex

WHEN VENOUS PRESSURE in a limb is elevated to pressures >25 mmHg, cutaneous, subcutaneous, and muscle vascular resistances increase within that region, resulting in a reduction in blood flow of ~40% (2, 5, 16, 17, 31, 32). This reflex has been termed the venoarteriolar response (VAR), because stretch receptors reported to be located in small veins are hypothesized to cause changes in arteriolar vascular tone “upstream” of the veins (15). During orthostasis, it has been suggested that as much as 45% of the increase in systemic vascular tone is due to the VAR, with the remaining 55% due to central reflex mechanisms elicited via baroreceptor unloading (15, 19, 20). An attenuated VAR may be one possible mechanism for a decrease in orthostatic tolerance after simulated microgravity

exposure (38) or in patients with the postural orthostatic tachycardia syndrome (34). In addition, it is likely that the VAR contributes to the maintenance of orthostatic tolerance in individuals with spinal cord transection (28, 33, 35). Thus the VAR appears to play a critical role in human cardiovascular control during orthostatic stress and is a key variable requiring careful quantification during examination of the effect of gravitational perturbations (10, 34, 35, 38).

The VAR has been evaluated during venous congestion induced by lowering the arm or leg below the heart level (5, 10, 14, 21, 25, 27, 33, 34, 36), during locally applied negative pressure (32), or during proximal cuff inflation (14, 15, 19, 24, 30, 34, 38). However, during cuff inflation, the consequent reduction in blood flow may not be due solely to the VAR, because cuff inflation uniquely decreases local perfusion pressure between arteries and veins, which may reduce blood flow in the absence of VAR-induced vasoconstriction. Surprisingly, the hemodynamic effect of cuff inflation on the assessment of the VAR has not been examined. Moreover, limb dependency may engage the myogenic reflex (6, 9, 22), as well as the VAR.

The purpose of this study was to dissect the relative contribution of arteriovenous hemodynamics, the VAR, and the myogenic reflex to the vasoconstriction induced by venous congestion. To accomplish this objective, we compared changes in forearm and calf skin blood flow (SkBF) during cuff inflation and limb dependency at the sites where the VAR was blocked by local anesthesia (1, 5, 14, 15, 19, 20, 32, 36, 37) and at unblocked sites.

METHODS

Subjects. Twelve healthy subjects (7 males and 5 females; age 35 ± 9 yr, mean \pm SD; height 171 ± 11 cm; weight 68.0 ± 14.9 kg) participated in this study. The study was performed in accordance with the Declaration of Helsinki, and all subjects signed an informed consent form approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas.

Protocol. The topical anesthetic eutectic mixture of local anesthetics (EMLA cream, 2.5% lidocaine, and 2.5% prilocaine; AstraZeneca, Wilmington, DE) was placed on both forearm and calf skin to block neurally mediated skin vasoconstriction and was covered with a Tegaderm dressing at least 2 h before the experiment. After that period of time, the dressing and the EMLA cream were removed. The effectiveness of the cream was assessed by testing blockade of tactile sensation from that area.

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The experiment was carried out 2–4 h after subjects ingested a light meal in a quiet, environmentally controlled laboratory with an ambient temperature of ~25°C. SkBF was measured during limb dependency, and cuff inflation was measured over areas where the VAR was blocked with EMLA cream (EMLA sites) and over areas of the contralateral forearm and calf intact skin (control sites). After establishment of stable SkBF was observed (usually 20–30 min supine), baseline data were collected for 2 min. Limb dependency or cuff inflation was then applied for 2 min, and measurements were repeated. After a sufficient recovery period (at least 2 min, when SkBF returned to the baseline level), baseline data collection was repeated. The alternative intervention (cuff inflation or limb dependency) was then applied. Choice of limb (right or left) for the EMLA sites, the order of the measurement at the EMLA and control sites, calf, and forearm, and the order for limb dependency or cuff inflation were randomized and counterbalanced among subjects.

Cuff inflation was set at 40 mmHg (Hokanson), which increases venous pressure to a similar magnitude (4, 11, 13). Because limb venous pressure in supine humans ranges from 7 to 12 mmHg (mean value ~10 mmHg) in forearms and from 10 to 20 mmHg (mean value ~15 mmHg) in legs (4, 26, 28), the increase in venous pressure by cuff inflation is estimated to be ~20–30 mmHg. Because cuff inflation to 40 mmHg is lower than diastolic pressure, limb arterial pressure is not affected significantly (12), and local perfusion pressure (arterial minus venous) decreases in accordance with the increase in limb venous pressure.

Arm or leg dependency was engaged by lowering the subject's arm or lower leg off the edge of the table such that the sites of SkBF measurement were 30 ± 3 (range 25–37) and 30 ± 4 (range 23–36) cm below the heart level, respectively, to match the increase in venous pressure during cuff inflation. With limb dependency, transmural pressure in the arteries increases in accordance with the hydrostatic pressure gradient between the heart and the limb (7, 28). Acutely, venous pressure may not increase proportionally to the same hydrostatic pressure gradient, because the venous valves restrict the backward flow. However, as blood continues to flow from the arteries into the dependent veins, they are filled up with blood and the venous valves are forced open in a heartward progression until there is an uninterrupted hydrostatic column between the central circulation and the limbs (28). Thus, once all venous valves are open, the venous transmural pressure is the sum of the dynamic pressure and the hydrostatic pressure, the same as in the arteries (28). Therefore, the premise of this study (and the VAR) is that there is no net change in perfusion pressure in the limb during limb dependency.

Measurements. SkBF was measured via laser-Doppler flowmetry (Perimed, Järfälla, Sweden). A laser-Doppler flow probe was placed

within the region of anesthesia for the EMLA sites or a similar region without anesthesia on the contralateral forearm or calf for the control sites. Local temperature was controlled at 34°C via a local heating element (Perimed). The typical error of repeated measurements of the assessment of the VAR (relative decrease in SkBF from baseline) with leg dependency in our laboratory is 14.8%. Heart rate (HR) was measured by lead II of the electrocardiogram (Hewlett-Packard), and beat-by-beat arterial blood pressure (BP) was obtained by finger photoplethysmography (Finapres; Ohmeda) with the finger placed at the heart level. SkBF, HR, and BP data were recorded at a sampling frequency of 250 Hz via a commercial data acquisition system (Biopac, Santa Barbara, CA). Beat-to-beat values of HR, systolic (SBP), and diastolic BP (DBP), were obtained using a custom program for peak detection. Beat-to-beat values of mean arterial pressure (MAP) were calculated as (SBP – DBP)/3 + DBP. The last 20 s of data for each 2 min of measurement were averaged and used for analysis. Also, arm BP was measured before each baseline measurement by electrospgmomanometry (Suntech), with a microphone placed over the brachial artery to detect Korotkoff sounds.

Estimation of skin vascular resistance. To determine whether a decrease in SkBF during cuff inflation or limb dependency was associated with local vasoconstriction, we estimated an index of skin vascular resistance (SkVR) as equal to (Pa – Pv)/SkBF, where Pa is arterial pressure and Pv is venous pressure (11). At baseline, Pa was assumed equal to MAP obtained by finger photoplethysmography and Pv was assumed equal to 10 mmHg (range from 7 to 12 mmHg) in the forearm and 15 mmHg (range from 10 to 20 mmHg) in the leg (4, 26, 28). During cuff inflation, Pa was equal to MAP and Pv was 40 mmHg (inflation pressure) (4, 11, 13, 34). During limb dependency, Pa and Pv were assumed to increase similarly depending on the distance between the measuring site and the heart level (18, 28).

Data analysis and statistics. Data are expressed as means ± SD for 12 subjects. SkBF was normalized to the baseline value and is presented as a percent change from baseline (%ΔSkBF) (5). The effects of local anesthesia, limb dependency, and cuff inflation on measured variables were determined using two-way ANOVA with repeated measures. Subsequent post hoc tests to determine significant differences in the various pairwise comparisons were performed using Bonferroni corrected *t*-tests. All statistical analysis was performed with a personal computer-based analysis system (SigmaStat 3.00; SPSS).

RESULTS

HR and MAP did not change during limb dependency or cuff inflation (Table 1). Original tracings of SkBF from a

Table 1. Changes in skin blood flow, estimated skin vascular resistance, heart rate, and mean arterial pressure during cuff inflation and limb dependency at control and EMLA-treated sites

	Cuff Inflation				Limb Dependency			
	Control sites		EMLA sites		Control sites		EMLA sites	
	Baseline	Inflation	Baseline	Inflation	Baseline	Dependency	Baseline	Dependency
<i>Forearm</i>								
SkBF, AU	78 ± 32	30 ± 10*	89 ± 39	59 ± 28*†	71 ± 37	38 ± 16*	97 ± 48	97 ± 63*‡
Estimated SkVR, AU	1.17 ± 0.55	1.67 ± 0.53*	1.07 ± 0.59	1.07 ± 0.71†	1.33 ± 0.65	2.46 ± 1.00*‡	0.99 ± 0.49	1.16 ± 0.70†
HR, beats/min	65 ± 11	64 ± 11	65 ± 11	66 ± 11	67 ± 12	64 ± 11	67 ± 11	66 ± 11
MAP, mmHg	86 ± 13	87 ± 14	87 ± 16	89 ± 14	88 ± 14	89 ± 14	89 ± 14	90 ± 15
<i>Calf</i>								
SkBF, AU	84 ± 45	35 ± 12*	119 ± 45	77 ± 42*†	85 ± 41	49 ± 23*‡	111 ± 43	114 ± 70*‡
Estimated SkVR, AU	1.07 ± 0.46	1.44 ± 0.43*	0.67 ± 0.32	0.75 ± 0.39†	1.03 ± 0.46	1.80 ± 0.81*	0.76 ± 0.36	0.90 ± 0.60†
HR, beats/min	66 ± 10	66 ± 10	66 ± 12	66 ± 11	66 ± 13	66 ± 13	66 ± 12	66 ± 12
MAP, mmHg	87 ± 10	86 ± 11	84 ± 9	85 ± 7	86 ± 11	87 ± 13	87 ± 11	89 ± 7

Values are means ± SD, *n* = 12. EMLA, eutectic mixture of local anesthetics; SkBF, skin blood flow; SkVR, skin vascular resistance; AU, arbitrary units; HR, heart rate; MAP, mean arterial pressure. **P* < 0.05, compared to baseline; †*P* < 0.05, compared with control sites, ‡*P* < 0.05, compared with cuff inflation.

representative subject during cuff inflation and limb (leg) dependency at the control site and the EMLA site are shown in Fig. 1. Forearm and calf SkBF during cuff inflation and limb dependency are shown in Table 1, and $\% \Delta \text{SkBF}$ in the forearm and the calf are presented in Fig. 2. There was no significant difference in baseline forearm and calf SkBF between the control and the EMLA sites before either limb dependency (forearm, $P = 0.195$; leg, $P = 0.208$) or cuff inflation (forearm, $P = 0.464$; leg, $P = 0.094$).

During limb dependency, SkBF at the control sites decreased by $45 \pm 9\%$ in the forearm and by $40 \pm 20\%$ in the calf (both $P < 0.001$), whereas it remained unchanged at the EMLA sites (forearm, $-5 \pm 23\%$, $P = 0.973$; calf, $-2 \pm 32\%$, $P = 0.825$). $\% \Delta \text{SkBF}$ during limb dependency was significantly smaller at the EMLA sites than at the control sites in both the forearm and the calf (both $P < 0.001$). On the other hand, during cuff inflation, SkBF at the control sites decreased by $57 \pm 13\%$ in the forearm and by $54 \pm 13\%$ in the calf (both $P < 0.001$). SkBF also decreased by $34 \pm 11\%$ in the forearm and by $37 \pm 17\%$ in the calf at the EMLA sites (both $P < 0.001$), although $\% \Delta \text{SkBF}$ during cuff inflation remained significantly smaller at the EMLA sites than at the control sites in both the forearm and the calf (both $P < 0.001$). $\% \Delta \text{SkBF}$ was significantly greater during cuff inflation than limb dependency at both the control sites (forearm, $P = 0.003$; calf, $P = 0.011$) and the EMLA sites (forearm and calf, $P < 0.001$).

The SkVR index in the forearm and the calf during cuff inflation and limb dependency is shown in Table 1. SkVR remained unchanged from baseline at the EMLA sites during

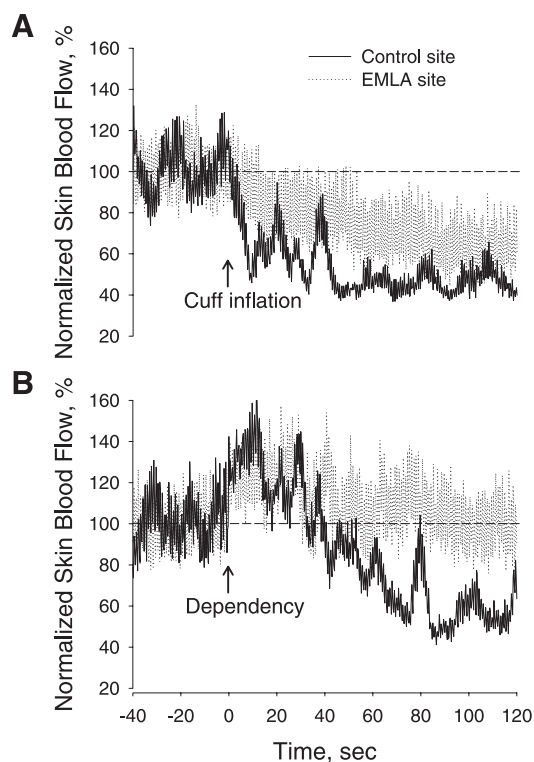


Fig. 1. Original tracings of skin blood flow from 1 representative subject, comparing normalized skin blood flow during cuff inflation (A) and limb (leg) dependency (B) at a control site (solid lines) and an EMLA (eutectic mixture of local anesthetics)-treated site (dotted lines). Data were originally sampled at 250 Hz; however, for display purposes, these data were resampled at 4 Hz.

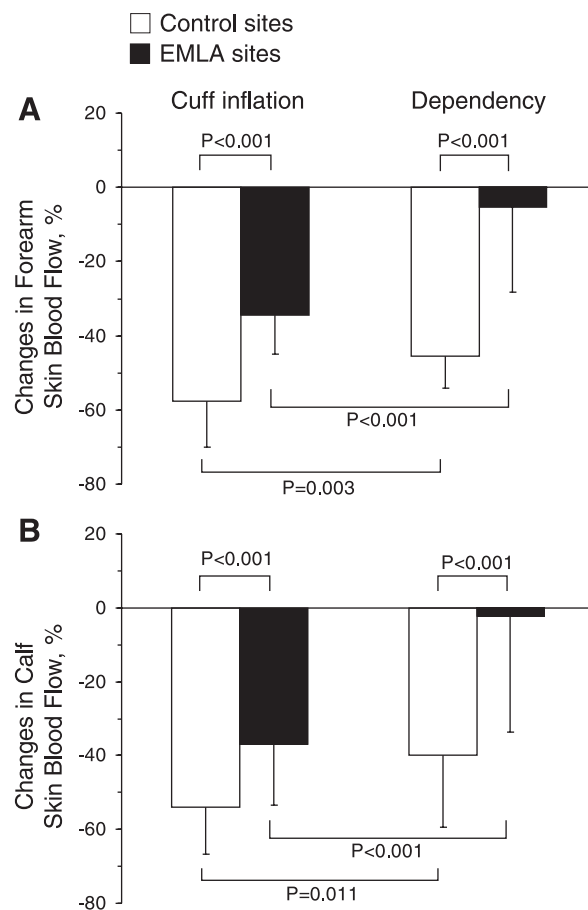


Fig. 2. Percent changes in skin blood flow in forearm (A) and calf (B) during cuff inflation (40 mmHg) and limb dependency (forearm, 30 ± 3 cm; calf, 30 ± 4 cm) at the EMLA-treated sites and contralateral control sites. Values are means \pm SD; $n = 12$ subjects.

cuff inflation (forearm, $-3 \pm 21\%$, $P = 0.986$; calf, $10 \pm 32\%$, $P = 0.218$), as well as limb dependency (forearm, $12 \pm 21\%$, $P = 0.055$; calf, $14 \pm 36\%$, $P = 0.188$). SkVR increased at the control sites during both cuff inflation (forearm, $57 \pm 58\%$, $P = 0.004$; calf, $52 \pm 57\%$, $P = 0.011$) and limb dependency (forearm, $90 \pm 27\%$; calf, $87 \pm 67\%$; both $P < 0.001$), suggesting that the reduction in SkBF during cuff inflation at the EMLA sites was not associated with the VAR but with the decrease in perfusion pressure.

DISCUSSION

The major findings of the present study are that 1) forearm and calf SkBF at the VAR-blocked sites remained unchanged during limb dependency but decreased during cuff inflation; 2) decreases in forearm and calf SkBF were significantly greater during cuff inflation than during limb dependency at both the control sites and the blocked sites; and 3) forearm and calf SkVR at the VAR-blocked sites remained unchanged during cuff inflation, as well as during limb dependency.

VAR during limb dependency. The VAR is mediated through a local mechanism (1, 5, 8, 37), and the central nervous system is not necessary to evoke the response (20, 25). This construct is supported by the observations that the VAR persists during acute spinal and sympathetic neural blockade proximal to the

site of measurement (14, 15, 19, 20, 31, 36), in denervated skin flaps (39) and in areas distal to the lesion in spinal cord transection patients (2, 33, 35). In the present study, subjects remained otherwise supine, and there were no changes in HR or arterial pressure during each test; thus changes in SkBF during each method were not related to central baroreflex mechanisms.

During limb dependency, an increase in hydrostatic pressure (28) causes an increase in intravascular pressure within that region (7). Increased venous pressure, especially in the venula (5, 10, 21, 25, 27), has been shown to be related to the magnitude of vasoconstriction within that region produced by the VAR. The increased venous pressure is thought to activate stretch receptors located in small veins and to cause vasoconstriction via a sympathetic axon reflex (14, 15, 19, 36). Crandall et al. (5) found that the response is mediated by nonadrenergic, but neurally mediated, local mechanisms by demonstrating that cutaneous vasoconstriction during arm dependency was preserved in areas of skin treated with selective and nonselective α -adrenergic antagonists, as well as in areas of skin treated with bretylium tosylate, which blocks neurotransmitter release from adrenergic nerves (23).

The arterial myogenic response related to increases in arterial pressure may also contribute to the changes in systemic vascular resistance during orthostasis (21, 25, 27, 39) and to vasoconstriction during limb dependency (6, 9, 22). Although the exact signal transduction pathways underlining the myogenic response remain uncertain, it has been thought that vascular smooth muscle depolarization culminates in increased intracellular Ca^{2+} levels with mechanically induced Ca^{2+} entry via voltage-gated Ca^{2+} channels and subsequent smooth muscle vasoconstriction (6, 22). However, one recent study by Scotland et al. (29) suggested that in rat mesenteric arteries, elevation of intraluminal pressure is associated with generation of arachidonate metabolites, which, in turn, activates vanilloid receptors TRPV1 on C-fiber nerve endings, resulting in depolarization of nerves and consequent release of vasoactive sensory neuropeptides. This pathway then causes constriction of vascular smooth muscle by binding to tachykinin NK1 receptors. Regardless of the specific pathway and consistent with prior studies (5, 36), the skin vasoconstriction was completely blocked during limb dependency at the EMLA sites in the present study. EMLA-induced inhibition of vasoconstriction with limb dependency is not due to impaired vasoconstriction of vascular smooth muscle but, rather, to inhibiting local neural communication required for the local vasoconstriction (14, 15, 19, 36), because lidocaine treatment does not impair cutaneous vasoconstriction to local application of norepinephrine (5). Therefore, if the myogenic response contributes to vasoconstriction during limb dependency, the result of the present study also supports the idea that vascular sensory fibers are involved in mediating the myogenic response (29).

Changes in SkBF during cuff inflation. Cuff inflation at a pressure lower than diastolic pressure impedes venous return, resulting in venous congestion and subsequent increases in venous pressure equivalent to the inflated cuff pressure (4, 11). However, in contrast to limb dependency, this maneuver minimally affects the local arterial circulation (12), and thus the arterial myogenic response is not likely to be activated during cuff inflation (9, 21, 24, 26, 34). Therefore, this maneuver has

been used to estimate the VAR, independently of the arterial myogenic response (21, 24, 34, 38).

In the present study, we showed that forearm and calf SkBF at the EMLA sites decreased significantly during cuff inflation. In addition, $\% \Delta SkBF$ in the forearm and the calf was significantly greater during cuff inflation than limb dependency at both the control sites and the EMLA sites, despite the similar increases in venous pressure during each method. These results strongly indicate that the decrease in SkBF during cuff inflation is not solely related to the cutaneous VAR.

During venous congestion with cuff inflation, local perfusion pressure between arteries and veins decreases because venous pressure increases up to the cuff pressure (4, 11, 13) without changes in arterial pressure (12). In the present study, we found that the SkVR estimated from SkBF and local arterial and venous pressure remained unchanged at the EMLA sites during cuff inflation. This finding suggests that the observed decrease in SkBF during cuff inflation at the EMLA sites is not caused by the VAR but, rather, by the decrease in local perfusion pressure. On the basis of this observation, we shall assume that a similar portion of the decrease in SkBF during cuff inflation at the control sites also is caused by the same hemodynamic effect.

In contrast to the present findings, Henriksen and Sejrsen (19) reported that there was no reduction in skin blood flow at lidocaine-treated sites during cuff inflation of 40 mmHg. One possible explanation for the discrepancy in responses between the present and the prior study could be the difference in concentration of lidocaine or the volume administered. They injected a very large dose of lidocaine (1 ml of a 20 mg/ml solution) intracutaneously, and data collection began 20 min after the injection (19). It is possible that the high concentration of lidocaine could have caused pronounced vasodilation. In addition, 20 min may not be long enough to eliminate vasodilation associated with injection trauma (3, 5). The pro-

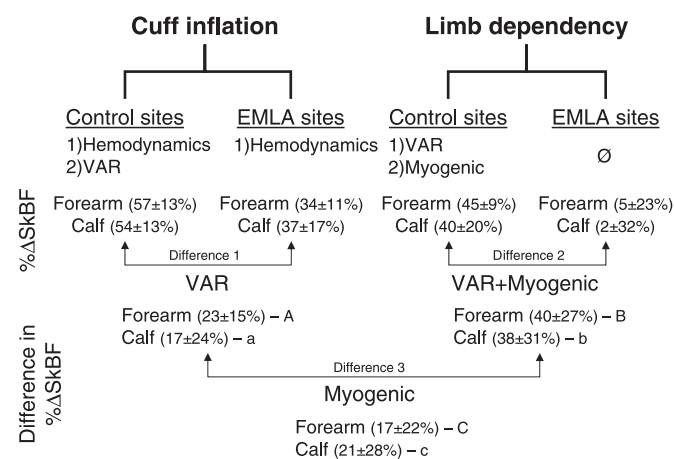


Fig. 3. Possible mechanisms of the decreases in skin blood flow during cuff inflation and limb dependency at the control sites and at the EMLA sites. The percent change in skin blood flow from baseline ($\% \Delta SkBF$) is presented. Also, the difference in $\% \Delta SkBF$ between the control and EMLA sites is calculated, which may reflect the magnitude of vasoconstriction due to the venoarteriolar response (VAR) during cuff inflation (difference 1) and to the VAR and the myogenic response during limb dependency (difference 2). The differences between cuff inflation and limb dependency in the solution of the difference in $\% \Delta SkBF$ between the control and EMLA sites may reflect the magnitude of vasoconstriction due to the myogenic response (difference 3).

nounced vasodilation would have opposed the reduction in perfusion pressure due to cuff inflation (5, 39). In contrast, we applied lidocaine by dermal application of EMLA cream at least 2 h before the experiment, and there was no significant difference in baseline forearm and calf SkBF between the control sites and the EMLA sites in the present study.

Implications. Possible mechanisms of the decreases in SkBF during each test in the present study are listed in Fig. 3. On the basis of the assumption that each mechanism of the decrease in SkBF is additive, during cuff inflation the decreases in SkBF at the control sites are caused by the hemodynamic changes plus the VAR, whereas those at the EMLA sites are solely due to the changes in hemodynamics. Therefore, it is reasonable to suggest that the difference in $\% \Delta \text{SkBF}$ between the control and EMLA sites during cuff inflation (*difference 1*, control sites minus EMLA sites: forearm, $23 \pm 15\% = A$; calf, $17 \pm 24\% = a$) may reflect the magnitude of vasoconstriction due to the VAR. In contrast, during limb dependency, the decreases in SkBF at the control sites are associated with the VAR and the myogenic response, whereas we had assumed that there are no such mechanisms active for the decreases in SkBF at the EMLA sites. Consequently, the difference in $\% \Delta \text{SkBF}$ between the control and EMLA sites during limb dependency (*difference 2*, control sites minus EMLA sites: forearm, $40 \pm 27\% = B$; calf; $38 \pm 31\% = b$) may reflect the magnitude of vasoconstriction due to the VAR and the myogenic response. Furthermore, the differences between cuff inflation and limb dependency in the solutions of the above equations (*difference 3*; forearm, $A - B = 17 \pm 22\% = C$; calf, $a - b = 21 \pm 28\% = c$) may reflect the magnitude of vasoconstriction due to the myogenic response. Ultimately then, we suggest that the percent contributions of the VAR and the myogenic response to the vasoconstriction during limb dependency are 58% ($A/B \times 100$) and 42% ($C/B \times 100$) in the forearm and 45% ($a/b \times 100$) and 55% ($c/b \times 100$) in the calf, respectively. Therefore, it also is suggested that the vasoconstriction due to the nonbaroreflex mechanisms during orthostasis may include the effect of the myogenic response (21, 25, 27, 39) by $\sim 40\text{--}60\%$.

Study limitations. There are at least four limitations to the present study. First, the cutaneous VAR was compared during limb dependency and cuff inflation by using laser-Doppler flowmetry. We recognize that the cutaneous vasculatures do not play an important role in blood pressure regulation during orthostasis under normothermic conditions. However, by assessing SkBF during the perturbation, it is possible that important information can be obtained that might provide a clue as to what is occurring in vascular beds that are more important to blood pressure regulation during orthostasis but are less accessible. Second, we did not measure local Pv and Pa directly. Hence, we could not distinguish the exact proportion of the decrease in SkBF during cuff inflation at the control sites that was caused by a reduction in perfusion pressure. Third, we assumed (but cannot prove) that the increase in transmural pressure from hydrostatic pressure gradients during limb dependency was the same in the arteries and the veins. Our results, which estimated SkVR did not change during limb dependency at the EMLA sites, argue in favor of this assumption. It should be noted that a dissociated increase in intravascular pressure between the arteries and the veins from supine to sitting position has been reported from direct measurements in the hallux (7). However, the measurements in that study were

performed after at least half an hour, which was considerably longer than the short (minutes) period of limb dependency in the present study and in previous reports (5, 10, 14, 21, 25, 27, 33, 34, 36). Direct measurements of transmural pressure in the arteries and the veins at the extremities during limb dependency within a few minutes are necessary to clarify this question. Fourth, we calculated the contributions of the VAR and the myogenic response to the vasoconstriction during limb dependency based on the assumption that each mechanism of the decreases in SkBF during cuff inflation and limb dependency is additive (Fig. 3). However, this assumption needs to be verified in future studies.

In conclusion, a decrease in skin blood flow assessed during venous congestion with the use of cuff inflation is not solely due to the cutaneous VAR but, rather, to changes in regional hemodynamics, with a decrease in local perfusion pressure between arteries and veins. Thus assessment of the VAR from a decrease in local blood flow with the use of cuff inflation overestimates the magnitude of the response and should therefore be performed cautiously. The effects of hemodynamics during cuff inflation may be minimized when the local vascular resistance is calculated and used to evaluate the VAR. Finally, from both techniques, we calculated that during venous congestion induced by limb dependency (in the calf), $\sim 45\%$ of the nonbaroreflex vasoconstriction is induced by the VAR and $\sim 55\%$ by the myogenic reflex.

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