Peripheral Assessment of Pheny lephrine-Induced Vasoconstriction by Laser Doppler Flowmetry and Its Potential Relevance to Homeostatic Mechanisms

David G. Silverman, MD; Alan B. Jotkowitz, MD; Michelle Freemer, BA; Viorel Gutter, MD; Theresa Z. O'Connor, PhD; Irwin M. Braverman, MD

Background. Cutaneous laser Doppler flowmetry enables monitoring of changes in skin perfusion by quantifying the phase shift of laser light induced by moving red blood cells under a fiberoptic probe. It thus can identify the presence of and response to a vasoconstrictive stimulus. However, aspects of the technique must be defined before it can be used with maximum effectiveness. We evaluated the responses of two different laser Doppler output, the concentration of moving blood cells (CMBC) and red cell flux (CMBC times cell velocity), and the responses at two sites of probe application, the finger and forearm, during systemic infusions of phentolamine.

Methods and Results. Eight healthy volunteers were monitored with a brachial blood pressure cuff, ECG, and laser Doppler flowmeter probes applied to the palmar surface of the fourth finger and volar forearm of the arm opposite the pressure cuff. After baseline readings were obtained, the subjects received three 10-minute intravenous infusions of phenylephrine at rates of 0.4, 0.8, and 1.6 μg · kg⁻¹ · min⁻¹. The two parameters, flux and CMBC, trended similarly. Flux and CMBC at the finger declined significantly in response to each infusion (P<.05 using repeated-measures ANOVA with Duncan's multiple range test). In contrast, flux and CMBC of the forearm had highly variable responses, with an overall increase during each infusion (P<.05 for %Δ of forearm versus %Δ of finger readings during the 0.4 μg · kg⁻¹ · min⁻¹ infusion). Heart rate declined significantly during each infusion, consistent with a baroreceptor-mediated response, even though systolic and diastolic blood pressures each increased by less than 2 mm Hg during the 0.4 μg · kg⁻¹ · min⁻¹ infusion.

Conclusions. As expected, laser Doppler readings at the finger decreased during infusion of an α₁-agonist. Although, like the digital vessels, forearm vessels have the potential to constrict, the increases in forearm readings suggest that these vessels are highly susceptible to homeostatic responses. The increase in CMBC (a parameter that is sensitive primarily to local changes in vascular caliber) suggested vasodilation of the underlying vessels. The forearm vasodilation and the concomitant decline in heart rate most likely represented vagally mediated baroreceptor activity, which was altered even though blood pressure changed minimally during the 0.4 μg · kg⁻¹ · min⁻¹ infusion. Thus, integrated assessment of skin perfusion at the finger and forearm may provide valuable information about the direct and indirect effects of a vasoactive stimulus. The present application of laser Doppler flowmetry suggests activation of vasodilatory reflexes despite minimal changes in blood pressure. (Circulation. 1994;90:23-26.)

Key Words: • Doppler flowmetry • phenylephrine • baroreceptors • vasoconstriction

Documented vascular responses in the periphery may alert one to the potential for significant alterations in the perfusion of vital organs. For example, stimuli that induce peripheral vasoconstriction may induce constriction of coronary vessels, most notably atherosclerotic vessels that have lost their ability for endothelium-dependent relaxation. Noninvasive monitoring of cutaneous perfusion by laser Doppler flowmetry may be helpful in this context. The technique, which primarily monitors flow in the arteriolar-capillary network 500 to 700 nm below the surface, quantifies the frequency shift of laser light as a result of moving red blood cells (RBCs) in the vessels under a 1-mm² fiberoptic probe. Although it is highly sensitive to movement, positioning, and the myriad factors that may alter skin perfusion,1-3 the laser Doppler should be well suited for assessing the changes in perfusion induced by a given insult as long as the probe is affixed to a single site and stable study conditions are maintained.4 However, certain aspects of this technique remain to be defined before it can be used with maximal effectiveness to monitor the effects of a vasoconstrictive stimulus. The present investigation was undertaken to evaluate means of data output and probe placement and to determine if it would be beneficial to integrate the data provided by different output parameters at different sites.

The standard laser Doppler output, RBC flux, is the product of the number of moving RBCs in the microcirculatory vessels under the monitoring probe (ie, the number that cause a Doppler shift) and their velocities (ie, the magnitude of the shift). A relatively untested laser Doppler output, the concentration of moving blood cells (CMBC) simply measures the number of moving RBCs in the vessels under the fiberoptic probe.5,6 Within the wide range of velocities that generate a Doppler shift, the actual
speed of RBC movement does not influence the CMBC value. Instead, CMBC primarily is sensitive to the caliber and hematocrit of the vessels under investigation. Because flux equals CMBC times velocity, we anticipated that flux and CMBC would respond similarly during infusion of a drug that primarily affected vascular caliber (eg, phenylephrine).

As indicated above, the laser Doppler should be affixed to the skin when the device is used to monitor changes in cutaneous perfusion. However, the commonly selected options for probe placement, the palmar surface of the finger and the volar forearm, differ with respect to their vascular anatomy, innervation, function, and responsiveness. We anticipated that they would not necessarily constrict to the same degree in response to systemic infusion of an \(\alpha_1\)-receptor agonist.

### Methods

With institutional review board approval and informed written consent, eight healthy male volunteers were studied in an isolated study room with temperature maintained at 22° to 24°C. An intermittent oscillometric brachial blood pressure monitor (Dinamap 1846SX, Critikon) was placed on the right arm, ECG leads were applied, and a 20-gauge catheter was inserted into the left hand for subsequent drug infusion. The fiberoptic probes of two identical laser Doppler flowmeters (Periflux PF 2B, Perimed) were applied to the palmar surface of the left fourth finger and to the left volar forearm. The latter entailed mapping, which was performed by placing the forearm probe successively for 30 seconds at 30 contiguous 1-mm² sites delineated by a plastic grid. The probe then was affixed to the site with the greatest flux value to provide proximity to an arteriole in the superficial horizontal plexus. Laser Doppler outputs (millivolts) were recorded continuously through an analogue-to-digital converter (Metabyte DAS-16F Data Acquisition System, Keithley Metabyte Corp) to an interfaced computer equipped with acquisition software (Snapshot Storage Scope Software, HEM Data Corp).

After a 10-minute baseline period, phenylephrine was infused at 0.4, 0.8, and 1.6 \(\mu g\cdot kg^{-1} \cdot min^{-1}\) for 10 minutes with a 15-minute interval between infusions. The subject was not informed as to the time of drug infusion. The infusion-induced changes in flux and CMBC at each site were determined beginning 2 minutes after onset of each infusion. The change in each parameter from baseline (at the three different doses) as well as the relative changes among parameters (at each dose) were analyzed using repeated-measures ANOVA with Duncan’s multiple range test. Potential risks were minimized by stopping an infusion if the heart rate declined by \(\geq 15\%\) or if the blood pressure increased by \(\geq 30\%\).

Changes in blood pressure and heart rate were not selected as primary end points during design of the present investigation; however, they were assessed retrospectively to determine whether the changes in laser Doppler values were attributable in part to a baroreceptor response. The statistical significance of the minor changes in blood pressure during the 0.4 \(\mu g\cdot kg^{-1} \cdot min^{-1}\) infusion was analyzed using paired \(t\) test with a Bonferroni adjustment.

### Results

As illustrated in the Figure, finger flux and finger CMBC each declined significantly in response to the three infusions (\(P < 0.05\) versus baseline for each parameter during each infusion). Each of these parameters declined during each infusion in each subject. Although finger flux tended to decrease to a greater degree than finger CMBC during the 0.4 \(\mu g\cdot kg^{-1} \cdot min^{-1}\) infusion, the relative declines of finger flux and CMBC did not differ significantly during any of the infusions.

The responses of forearm flux and forearm CMBC essentially were opposite from those of their finger counterparts (Figure). However, the increase in these indices was inconsistent; the only significant difference from baseline was noted for the increase in arm flux during the 0.4 \(\mu g\cdot kg^{-1} \cdot min^{-1}\) infusion. There were no significant differences between %Δ forearm flux and %Δ forearm CMBC during any of the infusions. However, the differences between %Δ flux at the forearm and finger and between the %Δ CMBC at the forearm and finger were significant during the 0.4 \(\mu g\cdot kg^{-1} \cdot min^{-1}\) infusion.

Retrospective assessment of the changes in blood pressure (to determine if an increase may have activated a baroreceptor response) revealed that during the 0.4 \(\mu g\cdot kg^{-1} \cdot min^{-1}\) infusion, systolic and diastolic blood pressures each increased by an average of less than 2 mm Hg (\(P=NS\) versus baseline). The changes in pressure averaged \(\pm 3\) mm Hg during any given minute of the infusion. Despite the small change in blood pressure during this infusion, heart rate decreased significantly, having declined an average of 8% from the baseline value. In contrast to the negligible changes in pressure during the low-dose infusion, systolic and diastolic blood pressures increased by 7% during the 0.8 \(\mu g\cdot kg^{-1} \cdot min^{-1}\) infusion and by more than 10% during the 1.6 \(\mu g\cdot kg^{-1} \cdot min^{-1}\) infusion (which was aborted in 7 of the 8 subjects when the heart rate declined by 15%). Heart rate decreased by an average of 11% during the 0.8 \(\mu g\cdot kg^{-1} \cdot min^{-1}\) infusion and 12% before discontinuation of the 1.6 \(\mu g\cdot kg^{-1} \cdot min^{-1}\) infusion.

### Discussion

As expected, laser Doppler flux and CMBC at the finger consistently decreased in response to each of the phenylephrine infusions. This direct effect of the \(\alpha_1\)-receptor agonist was noted for finger flux and finger CMBC in each of the eight subjects. In contrast, forearm values tended to increase during each infusion. Changes at the forearm were less consistent than their finger counterparts (Fig-
As discussed below, they appear to have been due to homeostatic reflex mechanisms. The differences between the responses of the finger and forearm, which were significant during the 0.4 μg·kg⁻¹·min⁻¹ infusion, became less distinct during the larger infusions as systemic responses (eg, changes in blood pressure and heart rate) became more pronounced.

The finger vessels are richly innervated with adrenoceptors and thus are prone to α-mediated constriction. Although digital vasoconstriction is not necessarily indicative of constriction at other sites, it may constitute a valuable marker in certain contexts. Most notably, atherosclerotic coronary vessels are highly sensitive to α-adrenoceptor agonists (as well as to other inducers of digital vasoconstriction such as cold pressor testing and mental stress).

The disparity between the changes in finger and forearm readings may provide valuable information about homeostatic mechanisms in response to increased plasma concentrations of an α₁-receptor agonist. In contrast to the vessels of the glabrous skin of the finger, forearm vessels are under cholinergic as well as adrenergic regulation. The present changes in forearm values (as well as heart rate) are consistent with vasoconstriction and baroreceptor responses noted in other settings. Transmural stretching of the carotid sinus induced a 35% reduction in forearm cutaneous resistance and a 9% decline in heart rate.

Head-down body tilt induced an increase in forearm flow and a decrease in heart rate. The homeostatic nature of the vasoconstriction to phenylephrine was demonstrated by a report that the pressure increase induced by phenylephrine was markedly increased after vagal block with atropine. Alternatively, the baroreceptor response to standing induces forearm vasoconstriction, as evidenced by decreased laser Doppler flux. Of note, head-up and head-down tilt did not induce changes in finger blood flow; this is consistent with the apparent vasodilation of forearm but not of digital vessels in the present investigation. As will be discussed below with respect to the present findings, an appreciation of the relative changes in vascular caliber and regional flow (as provided by CMBC and flux) may be helpful in elucidating the local and systemic responses in the aforementioned settings.

The retrospective assessment of pressure changes was most illuminating in that it revealed that during the 0.4 μg·kg⁻¹·min⁻¹ infusion, the significant declines in finger flux and finger CMBC occurred without an accompanying change in blood pressure. Moreover, it revealed that the apparently reflexive change in heart rate and forearm perfusion occurred despite the absence of a pressure change. This is not consistent with the classic description of the baroreceptor response; however, it is not inconsistent with known physiological mechanisms. Low-pressure, volume-sensitive cardiopulmonary receptors may be activated in the absence of a pressure change; increased venous return, as may be induced by phenylephrine, can initiate such responses. In addition, there is laboratory evidence that phenylephrine and norepinephrine can affect baroreceptors directly (in the absence of a precipitating pressure or volume change).

Although we believe that the changes in forearm perfusion most likely represent a reflexive homeostatic response, other potential mechanisms may have contributed to the increase in cutaneous forearm perfusion. The local release of endothelium-dependent relaxant factor can be pronounced in forearm vessels; however, it is unlikely that a local homeostatic mechanism would “overshoot” to the extent of increasing forearm flow to the degree noted in the present study. Divergence of blood from constricted digital vessels also could have contributed to cutaneous forearm flow; however, the forearm muscle constitutes a relatively large vascular bed that should readily channel the diverted blood.

To the best of our knowledge, this is the first study to compare the relative responsiveness of CMBC and flux with a vasoconstrictive stimulus. The relative changes in these parameters may shed light on vascular responses and on the mechanisms associated with a change (or lack thereof) in a derived measure such as blood pressure. Both laser Doppler indices are sensitive to changes in vascular caliber; flux is far more sensitive than CMBC to RBC velocity. The greater decline in finger flux (versus finger CMBC) during the 0.4 μg·kg⁻¹·min⁻¹ infusion suggested a decline in flow velocity (as well as vessel caliber) consistent with the 8% decrease in heart rate in the absence of an offsetting increase in blood pressure. The comparable increases in forearm flux and forearm CMBC during the 0.4 μg·kg⁻¹·min⁻¹ infusion suggested that the increase in forearm perfusion was due predominantly to vasodilation rather than to increased flow velocity. The apparent interdose consistency of the forearm CMBC response suggested that forearm vasodilation was comparable at each of the three doses. The relative decline in forearm flux (compared with forearm CMBC) during the 0.8 and 1.6 μg·kg⁻¹·min⁻¹ doses was consistent with the decreases in heart rate and, hence, RBC velocity.

Conclusions

A noninvasive means of monitoring perfusion in the periphery may provide valuable information about the effects of a vasoactive stimulus. When the sites of application and output parameters are properly chosen and stable study conditions are maintained, laser Doppler flowmetry may be particularly helpful in delineating direct and indirect responses. Its use in the present study has identified digital vasoconstriction and suggested activation of the baroreceptor reflex by otherwise undetectable doses of an α-adrenoceptor agonist.

Acknowledgments

This work was funded by an American Heart Association Medical Student Research Fellowship (Dr. Jotkowitz, student; Dr. Silverman, preceptor) and NIH/GCRC grant RR00125. The authors wish to express their appreciation to John Elwood, CBE, Dean F. Sittig, PhD, and Jeffrey Clyman, MD, for biomedical and computing expertise and to Jacki Fitzpatrick for excellent secretarial assistance.

References


Peripheral assessment of phenylephrine-induced vasoconstriction by laser Doppler flowmetry and its potential relevance to homeostatic mechanisms.

D G Silverman, A B Jotkowitz, M Freemer, V Gutter, T Z O'Connor and I M Braverman

Circulation. 1994;90:23-26
doi: 10.1161/01.CIR.90.1.23

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/90/1/23

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/