Commentaries on Viewpoint: The human cutaneous circulation as a model of generalized microvascular function

INVITED COMMENTARY ON VIEWPOINT BY HOLOWATZ ET AL

TO THE EDITOR: The paper by Holowatz et al. (3) may be advancing our ability to achieve the elusive goal of using readily accessible vessels, such as in the skin, as diagnostic surrogates for the vessels supplying internal organs (especially the heart and brain). This advance would allow minimally invasive detection of early, presymptomatic disease of the arteries in the critical organs. The new technique applied by them advances the ability to monitor skin microcirculation, but it is not clear that they have demonstrated that skin circulation is quantitatively representative of the vessels supplying critical internal organs in that same individual. For example, Aboyans et al. (1) recently reconfirmed that large and small vessels do show similarities as far as atherosclerosis is concerned, but Haltmayer et al. (2) showed clearly that different vessel beds respond differently to the same risk factors. The skin circulation consists predominantly of microvessels, which raises the question as to their propensity for being affected by atherosclerosis (or other systemic diseases such as hypertension or diabetes mellitus) just like the microvessels of the critical organs or, perhaps better still, the larger, conduit vessels that most often result in massive infarctions due to their blockage. Hence, the onus is on the authors to use their technique to show that indeed they can apply it to skin microvessels as indicators of disease in vessels of the internal organs in the same individual.

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COMMENTARY ON VIEWPOINT: THE HUMAN CUTANEOUS CIRCULATION AS A MODEL OF GENERALIZED MICROVASCULAR FUNCTION

TO THE EDITOR: Skin blood flow has long been studied as a key element of thermoregulatory responses in humans. Reflex and local mechanisms involved in cutaneous microvascular responses to temperature have proven to be not only complex and fascinating in and of themselves, but also influenced by a variety of nonthermoregulatory influences including age, reproductive hormones, circadian rhythms, and many others (1, 3, 4). Although the study of skin blood flow has often been the focus of thermoregulatory and exercise physiologists, Holowatz and colleagues (2) focus our attention on the utility of the cutaneous circulation as a more generalized model for human microvascular function in their Viewpoint. As the authors point out, the cutaneous circulation is accessible to the in-depth study of mechanisms of microvascular dilation and constriction with minimally invasive procedures. In particular, the development of specific pharmacological agonists and antagonists in combination with procedures such as intradermal microdialysis and laser-Doppler measurement of microvascular perfusion allow for the study of basic mechanisms in the context of an integrated physiological system, i.e., an intact human being. This has led to the study of mechanisms of blood flow control with a depth that may previously have been reserved for in vitro systems and isolated blood vessels. Importantly, the mechanisms studied provide insight into microvascular function, in contrast to techniques such as flow-mediated dilation of the brachial artery, which provides information about a conduit vessel, in which mechanisms of vasodilation are distinct from those of the microcirculation.

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COMMENT ON “THE HUMAN CUTANEOUS CIRCULATION AS A MODEL OF GENERALIZED MICROVASCULAR FUNCTION”

TO THE EDITOR: Authors adequately discuss whether skin microcirculation is a model of generalized microvascular function (2). However, this issue and other related aspects (which are the most specific test and the most appropriate body site for skin microcirculatory investigation?) remain to be defined, due to the inconclusive results of the available studies (3–5). For instance, a good correlation between the vasodilator impairment in peripheral and heart microcirculation was demonstrated in patients with microvascular angina using strain-gauge plethysmography (4); however, this method explores not only skin but also arm skeletal muscle microcirculation. Some skin laser-Doppler parameters resulted more specific than brachial flow-mediated vasodilation in predicting coronary disease (5) and they showed a good correlation with cardiovascular risk factors (3); however, their correlation with cardiac microcirculation was not investigated in both studies (3, 5). Moreover, as emphasized by the authors, the different methods used to induce skin vasodilatation act via multiple mechanisms. This prevents evaluation of the specific mechanisms controlling skin microcirculation, such as the endothelial-, sympathetic-, and myogenic-dependent mechanism. These mechanisms can be selectively investigated by means of power spectral analysis of skin laser-Doppler signal. In this respect, this method has been used with good results in arterial hypertension, diabetes, and peripheral arterial disease (6). Overall, skin laser-Doppler mi-
crocirculatory stimulation tests showed a good correlation with age and life style parameters or with the severity of the above mentioned pathological conditions (1, 6), suggesting their intensive use in health and diseases.

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ANALYZING THE OSCILLATORY COMPONENTS OF THE DYNAMICS OF BLOOD FLOW

TO THE EDITOR: Global approaches to the assessment of physiological functions such as the dynamics of blood flow are critical to the development of our understanding of integrated function. Laser-Doppler measurements of human cutaneous circulation do provide an excellent model for microvascular function (2) but the generalized nature of these signals, if analyzed in depth, is one of their strengths not a weakness. The challenge associated with multiple time-differentiated mechanisms can be overcome through the use of nonlinear methods of signal analysis, such as wavelet transform, to investigate the complex oscillations in microvascular blood flow (1, 4). Blood flow in the capillaries is a dynamic oscillatory process that is the result of the integration of at least six oscillatory components (4). These components can be investigated using the laser-Doppler blood flow signals yielding information about the relative contribution of the six oscillatory systems to the overall dynamics of blood flow in the capillaries of an individual (1). Changes in these relative contributions associated with specific disease states or clinical interventions can then be identified (3, 5). An important point is that changes in the relative contributions of the six oscillatory components to the overall dynamics of blood flow can occur in the absence of any changes in the average flow rate. Thus complex in-depth analysis of the signals, with or without pharmacological perturbation, is more likely to reveal underlying pathologies than the simple average values of blood flow rates.

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INVITED COMMENTARY ON “THE HUMAN CUTANEOUS CIRCULATION AS A MODEL OF GENERALIZED MICROVASCULAR FUNCTION”

TO THE EDITOR: Lacy Holowatz and her colleagues (3) present an intriguing viewpoint on the use of the skin microcirculation as an accessible surrogate to study generalized microvascular dysfunction. The authors outline several outstanding studies from their lab, as well as others, using laser-Doppler flowmetry in combination with microdialysis to investigate cutaneous microvascular responses to reactive hyperemia in coronary artery disease and with healthy human aging. However, a clear association between altered cutaneous microvascular function and specific microvascular or conduit artery dysfunction in other vascular beds (e.g., the coronary or skeletal muscle circulations with occlusive arterial disease) is lacking. Important challenges raised by the authors were that control of the cutaneous circulation includes vasconstrictor and vasodilator neural pathways (1) coupled with multiple associated regulatory mechanisms; the combination of which will ultimately dictate any cutaneous vascular response. Another challenge to using the cutaneous microcirculation as a model may be its complex vascular network, which in human skin includes both nutritional and nonnutritional components (2). Nonnutritional cutaneous blood flow includes responses to several thermal and nonthermal stimuli. By some estimates, nutritional blood flow may only represent 5–10% of the laser-Doppler signal, with the remainder nonnutritional (4). When generalizing from skin microvascular function, we must consider how (and if) nonnutritional blood flow is affected by various disease states, as some vascular disease pathology may be specific to nutritional blood flow. Thus investigations should focus on comparisons between altered cutaneous microvascular function and dysfunction in vascular beds that only receive nutritional blood flow, e.g., cardiac and skeletal muscle.

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COMMENTARY ON “THE HUMAN CUTANEOUS CIRCULATION AS A MODEL OF GENERALIZED MICROVASCULAR FUNCTION”

TO THE EDITOR: The forearm perfusion technique and the reactivity of coronary vessels are the methods usually used to explore microvascular function in patients (2). Regarding the contribution of endothelial dysfunction to the pathophysiology of cardiovascular diseases, the development of less invasive methods is a great challenge for both clinical risk assessment and monitoring responses to treatment. Recently, Dr. Holowatz (4) proposed the measurement of skin blood flow by laser-Doppler flowmetry as a minimally invasive method for assessing microvascular endothelial function. However, whether changes in generalized microvascular endothelial function evidenced by the forearm perfusion technique or coronary vessel reactivity are really associated with an impairment of skin vessels reactivity remains to be demonstrated. Moreover, the conclusions drawn from changes in skin blood flow may be confounded by the procedure used for inducing skin hyperemia. For instance, the contribution of NO to vasodilation is more important for thermal hyperemia than for hyperemia elicited by acetylcholine delivery or transient occlusion (3).

Nevertheless, the authors (5) identified for the first time the role of arginase in hypertension-associated endothelial dysfunction in humans. They showed that the delivery of an arginase inhibitor through an intradermal microdialysis probe increased NO-dependent skin hyperemia in hypertensive patients. This result has to be related to very recent data reporting that the administration of an arginase inhibitor to spontaneously hypertensive rats improved endothelial function at the microvascular level (mesenteric arteries) (1). Therefore, the laser-Doppler flowmetry of the skin seems to be a promising tool for exploring microvascular function of resistance vessels.

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