VIEWPOINT

The human cutaneous circulation as a model of generalized microvascular function

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CARDIOVASCULAR DISEASES affect ~80 million people and are collectively the leading cause of death in the United States (3). Impaired endothelial vascular signaling leading to endothelial dysfunction is one of the earliest vascular changes in the pathogenesis of cardiovascular disease. Endothelial dysfunction is a globalized systemic disease process consisting of attenuated endothelium-dependent vasodilation, augmented vasoconstriction, and microvessel structural remodeling that occurs simultaneously in multiple vascular beds (2). Remodeling of vascular structure and an attendant loss of endothelium-derived vasodilators, including nitric oxide (NO), may be the earliest pathological finding associated with cardiovascular disease (6, 16, 23).

There are several noninvasive measurement techniques to assess vascular function that are highly correlated with cardiovascular outcomes, including flow-mediated vasodilation, pulse wave velocity, and carotid intima media thickness (3). These techniques are useful for monitoring disease progression and the efficacy of clinical treatment modalities, but primarily evaluate conduit artery function, offering little insight into the underlying mechanisms of systemic microvascular pathology.

In recent years the cutaneous circulation has emerged as an accessible and potentially representative vascular bed to examine the mechanisms of microcirculatory function and dysfunction (2, 14a, 26, 30). Pathology-induced vascular dysfunction (including impaired endothelium-dependent vasodilation) is evident in the cutaneous circulation (5, 11, 12, 17) and may mirror generalized systemic vascular dysfunction in magnitude and underlying mechanisms (2, 14a, 25, 30). Furthermore, minimally invasive skin-specific methodologies make the cutaneous circulation a useful translational model for investigating mechanisms of vascular disease and providing preclinical data about the state of microcirculatory function in high-risk populations. To date, the skin has been used as a model circulation to investigate vascular mechanisms in a variety of disease states, including hypercholesterolemia (15), hypertension (5, 23), hyperhomocysteinemia (1), renal disease (30), Type II diabetes (28), peripheral vascular disease (24), atherosclerotic coronary artery disease (27), heart failure (8, 10), systemic sclerosis (4), and primary aging (14, 18, 32, 33).

The cutaneous circulation is the main effector organ for human thermoregulation and has a high vasodilatory reserve capacity in response to metabolic, thermal (reflex and locally induced), and pharmacological stimuli. Relative changes in skin blood flow over large areas of skin can be measured using laser-Doppler imagery to examine the spatial distribution of microvessel reactivity (20). Alternatively, laser-Doppler flowmetry can be used to measure dynamic changes in laser-Doppler flux over a small area of skin to vasoreactive stimuli. Cutaneous vasodilation or vasoconstriction can be elicited through postocclusive reactive hyperemia (35), whole body heating (14), whole body cooling, local heating (18), local cooling (32), and the application specific vasoactive pharmacological agents by iontophoresis (1) or intradermal microdialysis. Iontophoresis delivers charged pharmacological agents in a vehicle solution to a localized area of skin using opposing electrical current. Intradermal microdialysis is a minimally invasive technique that permits the bidirectional exchange small molecular weight substances through a porous cellulose membrane. Microdialysis offers the advantages of continuous drug (or combination of drugs) delivery to a small localized area of skin while measuring the effects of that drug via laser-Doppler flowmetry. Furthermore, small molecular weight substances in the interstitium can be sampled and analyzed from the microdialysis effluent. With intradermal microdialysis there are no confounding effects of electrical current-induced hyperemia as may occur with iontophoresis, but the potential confound of needle insertion trauma does exist with microdialysis. In addition to these techniques, digital power spectral analysis of frequency domains of the laser-Doppler flow meter signal can be performed to partition the vascular endothelial, myogenic, local sympathetic activity, hemodynamic, and respiratory influences on cutaneous microvascular reactivity (29). [For a detailed review of these methods refer to the recent review by Cracowski et al. (7).] Collectively, these minimally invasive approaches allow the targeted manipulation of the putative signaling pathways associated with cutaneous microvascular dysfunction in humans.

Our laboratory has examined age-associated deficits in thermoregulatory function, focusing on the mechanisms underlying impaired cutaneous vascular reactivity to thermal stimuli. We have used intradermal microdialysis paired with laser-Doppler flowmetry during whole body and/or localized application of heat and cold to pharmacodissect the signaling pathways involved in cutaneous vasodilation and vasoconstriction. Consistent with animal and in vitro human studies, we measured a decrease in NO-dependent vasodilation that can be...
augmented by either 1) inhibiting arginase, which competes for the common NO substrate, or 2) providing high-dose ascorbate supplementation. These results provided insight into the underlying mechanisms contributing to age-related impairments in NO bioavailability, implicating upregulated arginase activity (14) and increased oxidant stress (13). With regard to vasocostricter mechanisms, aged skin exhibits decreased adrenergic responsiveness (33) and a lack of redundant signaling pathways that mediate cutaneous vasocostriction. Increased Rho-kinase activity has been implicated as one of the major mechanisms mediating the proconstrictor vascular conditions commonly associated with aging, including hypertension, coronary and cerebral vasospasm, erectile dysfunction, and diabetes. In response to a skin-specific activation of the Rho-kinase pathway (local cooling) the aged cutaneous vasculature exhibits augmented Rho-kinase-dependent vasocostriction (32). Cumulatively, these findings in the aged cutaneous vasculature parallel results from studies examining similar aging mechanisms throughout the systemic vasculature, supporting the assertion that the cutaneous circulation is a useful surrogate for examining some mechanisms of generalized vascular dysfunction.

Essential hypertension is a pathology where noninvasive measures for evaluating vascular function may have value for early detection and prediction of disease course. Structural and functional alterations throughout the systemic peripheral resistance vasculature are hallmark maladaptations to the increased hemodynamic load of essential hypertension. Deficits in cutaneous vasoreactivity are measurable early in the progression of hypertensive vascular disease (11, 12, 17, 19, 22), and hypertrophy of the cutaneous resistance vasculature is predictive of future cardiovascular events (23). Although the cutaneous circulation does not likely contribute significantly to the total increase in systemic vascular resistance, we and others have measured significantly attenuated cutaneous vasodilation in response to localized (5) and systemic thermal stress (11, 12). Similar to the forearm muscle (31) and coronary circulations (34), we observed reduced NO-dependent vasodilation that can be augmented with high doses of the antioxidant ascorbate. Several different animal models of hypertension have shown that vascular arginase is upregulated in response to increased hemodynamic loads (9). We observed an increase in NO-dependent cutaneous vasodilation during arginase inhibition, suggesting that arginase is also upregulated in the human cutaneous circulation with hypertension (11). While these types of in vivo mechanistic human studies are in their infancy, these preliminary findings are promising for using minimally invasive techniques to assess microvascular dysfunction in the cutaneous circulation and for identifying new therapeutic targets for the treatment of hypertension.

One challenge associated with using the skin as a surrogate circulation is that skin-specific methodologies induce vasodilation and/or vasoconstriction via multiple, and often time redundant, mechanisms, i.e., they do not specifically isolate individual vascular signaling pathways. Instead they elicit an integrated cutaneous vascular response involving neural, endothelial, and vascular smooth muscle contributions. These complex interactions in vascular signaling are the nature of in vivo human integrative physiology, regardless of the vascular bed being studied. Because the available skin-specific techniques illicit vasoactive responses that involve multiple signaling pathways, they provide a global assessment of microvascular function.

In summary, the cutaneous circulation is an accessible and representative vascular bed for the assessment and pharmacodissection of mechanisms underlying vascular disease. There are a variety of minimally invasive, skin-specific techniques available to manipulate the putative signaling pathways associated with vascular pathology and to test integrative cutaneous vascular function. More research correlating pathology-induced changes in cutaneous vascular function with microcircular function in other vascular beds (coronary and renal) is needed to fully understand the implication of pathophysiologic vascular changes in disease states. In addition, research into the basic mechanisms that control cutaneous vascular responses in healthy populations is needed to fully understand the effects of pathology.

REFERENCES