PERSPECTIVES

Human cutaneous microvascular ageing: potential insights into underlying physiological mechanisms of endothelial function and dysfunction

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Attenuated human blood vessel reactivity, and an attendant loss of nitric oxide, is an independent risk factor associated with increased cardiovascular mortality and may be the earliest pathological finding associated with cardiovascular disease. Furthermore, vascular dysfunction resulting from decreased NO bioavailability is a systemic disease process that occurs simultaneously in multiple vascular beds affecting both the resistance and conduit vasculature (Abularrage *et al.* 2005).

In this issue of *The Journal of Physiology*, Mark Black and colleagues present findings from a timely study further demonstrating that the cutaneous circulation is an easily accessible, representative vascular bed for the *in vivo* assessment of microvascular function in humans (Black *et al.* 2008; Khan *et al.* 2008). Moreover, the cutaneous circulation has utility for the examination of therapeutic treatment modalities, including aerobic exercise, to improve microvascular function. These authors eloquently demonstrated that aerobic exercise training enhances cutaneous NO-dependent vasodilatation to skin-specific physiological and pharmacological stimuli in a previously sedentary healthy aged cohort of human subjects. The observed training-induced alterations in the mechanisms that regulate blood flow to the cutaneous microvasculature mirror systemic changes that also occur in the conduit vasculature.

The results of this study highlight the likelihood that there are several key mechanisms underlying reduced NO bioavailability in preclinical and clinical vascular dysfunction. These mechanisms include: (1) reduced substrate availability for NO synthesis through nitric oxide synthase (NOS), possibly through up-regulation of arginase or differential regulation of the discrete L-arginine microdomains, (2) reduced NOS cofactor availability (tetrahydrobiopterin) for the synthesis of functional NO, (3) a globalized increase in oxidant stress (Holowatz *et al.* 2007), and (4) augmented proconstrictor mechanisms including Rho-kinase (Thompson-Torgerson *et al.* 2007). Additionally, there is likely a significant degree of interplay between these key underlying mechanisms with differential contributions depending on the vascular disease state.

Black *et al.* nicely paired both a physiological and a pharmacological stimulus to examine NO function in sedentary aged humans. Interestingly, these authors found that the absolute magnitude of the vasodilator response to a physiological stimulus for NO-dependent vasodilatation (local heating) was similar among young control, aged sedentary and aged highly fit subjects. However, the contribution of NO (comparison between the control site and the NOS-inhibited site) to the rise in skin blood flow to local heating was attenuated in the sedentary aged subjects. This suggests that even in the preclinical sedentary aged vascular state other compensatory vasodilator mechanisms are up-regulated. Questions remain as to the identity and potential physiological impact of these up-regulated vasodilator mechanisms. However, the physiological significance of these altered pathways will likely become more evident when moving forward on the vascular disease state continuum when these compensatory mechanisms and redundancies are lost.

This study carefully demonstrated that exercise training augments NO-dependent vasodilatation; however, the specific underlying mechanism(s) that exercise training effects to result in greater NO bioavailability remains to be determined. These authors suggested that chronic exercise training likely has an impact on the balance of oxidant production and antioxidant clearing capacity leading to an overall decrease in oxidant stress. However, the precise enzymatic sources of oxidants, potential differences in antioxidant clearing mechanisms and how these may be altered with preclinical (primary ageing) and clinical vascular disease states is unclear. Additional experiments in the cutaneous microcirculation using skin-specific stimuli to target the putative signalling mechanisms involved in regulating NO bioavailability will be the key to understanding the way pathology and the impact of exercise training modify microcirculatory function in humans.

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