Mechanisms of Endothelial Dysfunction Induced by Aging
Role of Arginase I

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Impaired production or biological activity of nitric oxide (NO) released from vascular endothelium is a central mechanism of endothelial dysfunction.1 Large number of published studies demonstrated that endothelial dysfunction is a hallmark of aged endothelium.2 Currently, increased concentration of superoxide anion in vascular wall is considered a major mechanism of endothelial dysfunction caused by aging.3,4,5 Detrimental effect of superoxide anion on aged endothelium is mediated by its chemical reaction with NO leading to inactivation of NO and production of a very potent oxidant, peroxynitrite.5 At the present time, there is no consensus in the literature regarding the exact source(s) of superoxide anion in aged blood vessels. Endothelial enzymes known to be potent generators of superoxide anion include NADP(H) oxidase, xanthine oxidase, cyclooxygenases, uncoupled endothelial nitric oxide synthases, as well as respiratory chain enzymes in mitochondria.1 Besides increase in superoxide anion production, impairment of endothelial nitric oxide synthase (eNOS) enzymatic activity or reduced antioxidant defense capacity of endothelium may also contribute to elevation of superoxide anion concentration and subsequent endothelial dysfunction.3,5

Optimal intracellular level of amino acid L-arginine, a substrate for eNOS, is a critical factor required for normal biosynthesis of NO. Prior studies by Berkowitz and colleagues6 demonstrated that during aging, increased activity of arginase I, (arginase I and arginase II are enzymes that catalyze the hydrolysis of L-arginine to L-ornithine and urea; Figure), may compete for L-arginine with eNOS thereby causing reduced production of NO and endothelial dysfunction. This concept was further supported by the studies demonstrating that in aged arteries genetic inactivation of arginase I could restore NO biosynthesis in vascular endothelium7 leading to the proposal that inhibition of arginase may represent a novel therapeutic strategy in prevention and treatment of endothelial dysfunction induced by aging. Given the fact that aging is a major risk factor for development of cardiovascular disease and that there is no therapies aimed at modulating cardiovascular risk inherent to aging, understan

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peroxynitrite is a very potent oxidant of BH4.14 However, a role in loss of NO and pathogenesis of endothelial dysfunction in human blood vessels exposed to proinflammatory conditions in vivo.15 This observation together with reported propensity of aged blood vessels to express higher levels of proinflammatory cytokines16 suggest that contribution of arginase to endothelial dysfunction may depend on degree of vascular inflammatory response to aging. Further in vivo studies with selective inhibitors of arginase I, as well as better understanding of the mechanisms involved in regulation of arginase in aging human endothelium, will define importance and therapeutic value of arginase inhibition in prevention and treatment of cardiovascular disease.

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**References**


