Endothelin and Aged Blood Vessels
One More Reason to Get Off the Couch?

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dge is one of the most important risk factors for cardiovascular disease. For example, a 30-year-old male smoker with untreated hypertension, diabetes, dyslipidemia, and a strong family history of premature coronary heart disease (CHD) would have a 10-year coronary heart disease event rate of only 16% (“intermediate risk”) by Framingham criteria; however, given exactly the same risk profile for a 60-year-old, the risk climbs to >50%. Aging, particularly sedentary aging, leads not only to the development of atherosclerosis but also to ventricular and arterial stiffening. This reduces functional capacity and contributes to chronic diseases of the elderly, such as systolic hypertension or heart failure with a preserved ejection fraction. In the search for the underlying mechanism for this effect of sedentary aging, one common feature that has been identified universally in older men is an increased baseline vascular tone, which has both hemodynamic and metabolic consequences.

Although this age-related increase in vascular tone is mediated in part by a chronically elevated sympathetic α-adrenergic vasoconstriction, endothelial function also plays a critical role in vascular stability and the regulation of vasomotor function. The endothelium regulates vascular tone through the release of dilator and constrictor substances. Endothelin (ET)-1 is the most potent endothelium-derived constricting factor and influences peripheral vascular tone by interacting with ETA and ETB receptors on smooth muscle cells and the endothelium. Several animal studies have examined the profound effects of vascular aging on the ET-1 pathway and support a central role for ET-1 receptors on smooth muscle cells and the endothelium. In the present issue of Hypertension, Van Guilder et al present new and important information regarding the role of aging and physical fitness on the vasomotor effects of ET-1. Using a cross-sectional design in a small but carefully studied cohort of healthy sedentary younger and older men, Van Guilder et al examined forearm blood flow responses to intrabrachial infusion of ET-1, selective ETα receptor blockade, and dual ETα/β receptor blockade. The combination of these well-established pharmacological methods allows the quantification of both ET-1 production and the role of the individual ET receptors and, thus, has a distinct advantage over other indirect methods, such as plasma concentrations of ET-1. As such, this is the first study in humans adequately demonstrating a pivotal role of ET-1 in the regulation of forearm vascular tone with aging. Based on the constrictor action of ET-1 in older men, an enhanced ET-1 signal transduction mechanism may contribute to the elevations in skeletal muscle vascular resistance and, consequently, systemic vascular resistance. These changes in the ET pathway may partially explain the predisposition of older men to cardiovascular pathology.

But what are the mechanisms for this increased ET-1–mediated vascular tone with aging? Potential contributing factors include the synthesis of ET-1, sensitivity or numbers of ETα/β receptors, and/or changes in the activated pathways by the ET receptors. Previous studies in rat skeletal muscle and coronary vessels demonstrate indirect and direct evidence for a central role for the ETα receptor to explain the age-related increase in vascular tone. In addition, the characteristic sustained vasoconstriction of ET-1 after binding to its receptors is partly caused by the activation of protein kinase C, leading to an increased sensitivity of the contractile apparatus. Changes in this pathway were recently found to explain the increased ET-1–mediated vascular tone with aging.

A few caveats should be raised when placing these data in perspective. First, the age-related increase in ET-1–mediated vasoconstrictor tone as demonstrated by Van Guilder et al was found in the forearm, e.g., a vascular bed that demonstrates similar baseline forearm blood flow compared with younger individuals. Vascular territories characterized by an age-related increase in vascular tone (e.g., the lower legs or cerebral arteries) may be more or less affected by the ET-1 pathway. Caution should be used in extrapolating findings from the forearm to other vascular beds; indeed, even in different regions of skeletal muscle, lower limbs demonstrate markedly enhanced α-adrenergic vasoconstriction compared with upper limbs, presumably because of chronically elevated hydrostatic gradients.

In addition, it should be noted that only one dose of ET-1 was used in this study. Therefore, the authors could not construct full stimulus-response curves for ET-1 in their volunteers. It may be that, in fact, sedentary aging leads to a change in the operating point on this curve so that there is less reserve for further activation of the ET-1 pathway without an actual change in ET-1 responsiveness. In this regard, it is curious that the authors (and others) have found a decreased ET-1 responsiveness with aging and associate this observation with increased cardiovascular risk.
It would seem more intuitive that decreased responsiveness to a vasoconstrictor would prevent rather than provoke cardiovascular disease. Conversely, the vasodilation associated with ET-1 inhibition is strongly suggestive of increased background ET-1 vasoconstriction in the sedentary elderly; full pharmacological dose-response curves would sort this issue out definitively. Finally, it also was a bit surprising to see only forearm blood flow responses reported; the calculation of resistance or its inverse conductance would have been informative. The latter may be especially important in circumstances like the present study where large baseline differences in conductance may exist among subject groups. Future studies in this area should consider testing other vascular beds and use multiple doses to describe full pharmacological profiles with conductance as the primary response characteristic.

Even healthy aging is generally associated with 2 key processes, biological senescence and physical inactivity, both of which may contribute cardiovascular dysfunction. For example, 3 weeks of bed rest deconditioning in healthy young men resulted in a greater decrease in maximal oxygen response characteristic.

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Even healthy aging is generally associated with 2 key processes, biological senescence and physical inactivity, both of which may contribute cardiovascular dysfunction. For example, 3 weeks of bed rest deconditioning in healthy young men resulted in a greater decrease in maximal oxygen transport than 30 years of aging. Conversely, lifelong fitness prevented the cardiac and arterial stiffening observed with healthy but sedentary aging. Animal studies seem to suggest that the effect of the ET-1 pathway on vascular function might be a function of senescence rather than physical inactivity: 12 weeks of exercise in old rats improved vascular tone but not ET-1 responsiveness of the ET receptors.

In contrast to animal studies, Van Guildet al demonstrated that 3 months of exercise training (5 to 7 days a week, mainly walking at 65% to 75% of maximal heart rate) was sufficient to restore the age-related increase in ET-1–mediated vascular tone. Interestingly, they found that the vascular responses to exogenous ET-1 and selective/dual blockade of the ETA receptors in the older men after training were comparable to their ~36-year-younger peers. The significance of physical inactivity as a key determinant of the contribution of ET-1 to vascular tone is recently supported by another human in vivo study, which demonstrated that the contribution of ET-1 to baseline leg vascular tone in the extremely inactive legs of individuals with spinal cord injury is markedly increased (through ETA receptors). The link with physical inactivity is supported by the largely reversed ET-1–mediated vasoconstriction in these subjects after 6 weeks of exercise training. Taken together, the results of both of these studies suggest that physical inactivity plays a major role in the ET-1–mediated vascular tone in humans through an ETA receptor–dependent mechanism.

Not only does the ET-1 pathway influence vascular hemodynamics, but it also may participate in the pathogenesis and progression of several cardiovascular diseases: essential hypertension, atherosclerosis, heart failure, and pulmonary hypertension. This role is supported by short-term (hours to weeks) beneficial effects of selective and/or dual ETA receptor antagonists. However, the identification of physical inactivity as a major determinant of the ET-1 pathway emphasizes that inactivity, rather than the pathology of these specific cardiovascular diseases, may be a strong candidate to explain the ET-1–mediated elevated vascular tone in cardiovascular disease, which may be substantially reversible by training.

Despite the strong link between ET-1 and cardiovascular diseases, long-term pharmacological interventions with oral ET receptor antagonists in heart failure and hypertension demonstrate no additional beneficial effect of these agents. Interestingly, physical forces such as shear stress may be essential physiological stimuli for the ET-1 pathway, although exercise training (leading to changes in shear stress) attenuates the constrictive actions of ET-1. This view is at least supported by findings in healthy older subjects and in the extremely inactive legs of healthy spinal cord injury individuals. Therefore, a physiological approach, such as exercise training, may be more effective than a pharmacological one to diminish the ET-1–mediated effects on cardiovascular diseases. Van Guildet al are to be congratulated on a carefully performed and thoughtfully presented study that advances the understanding of the dynamics of regulation of vascular tone with aging and physical activity.

**Source of Funding**

This work was supported by the National Institutes of Health/National Institute on Aging grant R01 AG017479. D.H.J.T. is financially supported by The Netherlands Organisation for Scientific Research (NWO-grant 82507010).

**Disclosures**

None.

**References**

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Hypertension. published online June 18, 2007;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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World Wide Web at:
http://hyper.ahajournals.org/content/early/2007/06/18/HYPERTENSIONAHA.107.091686.citation

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