A Vascular Theory of Aging

David G. Le Couteur1,2 and Edward G. Lakatta3

1Centre for Education and Research on Ageing and 2ANZAC Research Institute, Concord Repatriation General Hospital, University of Sydney, New South Wales, Australia.
3Laboratory of Cardiovascular Science, Gerontology Research Center, National Institute on Aging, National Institutes of Health, Baltimore, Maryland.

Address correspondence to David G. Le Couteur, MD, PhD, ANZAC Research Institute, Concord RG hospital, University of Sydney, Sydney, NSW 2139, Australia. Email: david.lecouteur@sydney.edu.au

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Advancing age is unequivocally the dominant risk factor for atherosclerosis and its major clinical consequences of ischemic heart disease and cerebrovascular disease (1–4). For example, the Framingham score for the risk of coronary heart disease allocates seven points to men with ages between 70 and 74 years compared with only three points for men with severe hypercholesterolemia and hypertension and two points for the presence of diabetes mellitus and smoking (5). Many possible explanations for the association between age and vascular disease have been proposed (3), but it is not mediated by any simple association between chronological age and duration of exposure to other established risk factors. In fact, many studies have found that in very elderly people, the association between hypertension, hyperlipidemia, and health outcomes is reversed (6–8). Advancing age is a pivotal and independent risk factor for cardiovascular disease. Given the increasing age of the population and our success in managing other vascular risk factors in middle age, it is clear that future gains in preventing cardiovascular disease require an increased understanding of vascular aging (9).

It can be argued whether there is any fundamental difference between primary aging and secondary age-related disease (20–21). In the vascular system, there is a continuum from the universal findings of microvascular aging and age-associated alterations in the large arteries through to significant atherosclerosis and vascular disease present in many, but not all, older people (1–3,22). Many of the morphological and functional changes that occur in the blood vessels in humans and experimental animals overlap with those that occur in the early stages of hypertension and atherosclerosis (23). From the pragmatic clinical perspective, vascular aging is responsible for heart attack and stroke, which are the major causes of morbidity and mortality in older people, and vascular aging also appears to contribute to other geriatric conditions, such as dementia, sarcopenia, and osteoporosis. It is often overlooked that in his original exposition of the Free Radical Theory of Aging in 1956 (24), Harman proposed that the primary target of oxidative stress was the vasculature. Fifty years of research since has shown the importance of vascular aging and the inexorable link between advancing age and atherosclerosis. Vascular aging and age-related susceptibility to vascular disease are central and proximal steps in the pathogenesis of those conditions leading to much of the morbidity, disability, and mortality that accompany old age. The corollary is that we must invest in research into the biology of vascular aging in order to improve the quality and quantity of life for older people (9).
Advancing age has usually been considered to be an unmodifiable risk factor for atherosclerosis and therefore dismissed as therapeutically irrelevant in comparison with other risk factors, such as hypertension, hyperlipidemia, and smoking where effective interventions are available and widely promoted. The contributions of smoking, hyperlipidemia, diabetes mellitus, obesity, and hypertension to cardiovascular disease have been extensively quantified, and much of modern medical practice focuses on management of these risk factors. However, despite being a much more potent risk factor, aging has languished from the research perspective because it has been deemed irreversible and unmodifiable. However, in their review on vascular aging, Ungvari and colleagues (25) have shown that this attitude must be reconsidered. With the explosion in knowledge of the biology of aging blood vessels, advancing age has now become a genuine therapeutic target for the prevention of cardiovascular disease in older people (9). Furthermore, advancing age almost certainly interacts with other cardiovascular risk factors, such as nutrition, physical activity, and genetic factors. Differences in lifestyle may account for the substantial heterogeneity of arterial aging observed among individuals: successful aging versus usual aging versus unsuccessful aging.

Currently, the main research domains in biogerontology are oxidative stress, mitochondrial dysfunction, replicative senescence and telomeres, inflammation, apoptosis, and progenitor cell dysfunction. Ungvari and colleagues comprehensively document the impact of each of these putative aging processes on the vascular system and in doing so have shown that the vascular system is a prototypical aging tissue (25). However, it does have some unique aging changes: for example, nitric oxide and angiotensin II pathways are particularly important for vascular aging at the cellular level. Furthermore, increased arterial stiffness and vascular inflammation are particularly special features of old age that are very familiar to clinicians who care for older patients.

Ungvari and colleagues review current experimental therapeutic strategies to delay vascular aging, thereby indicating that aging can no longer be considered an unmodifiable risk factor for vascular disease. They propose that there are several approaches to gero-vasoprotection including novel anti-inflammatory agents acting on tumor necrosis factor-α, endocannabinoids, and the poly adenosine diphosphate ribose polymerase pathways; growth hormone and insulin-like growth factor-1; exercise; caloric restriction; and resveratrol. Resveratrol has been the subject of extensive research in aging because of its ability to recapitulate some of the beneficial effects of caloric restriction (26–28). Ungvari and colleagues describe studies showing the substantial vasoprotective effects of resveratrol in vivo and in vitro and argue that some of the beneficial cardiovascular effects of the Mediterranean diet are secondary to the fact that it is rich in resveratrol. Although pharmaceutical interventions to delay vascular aging show promise in the laboratory, the main intervention that could be recommended now to humans on the basis of evidence is regular exercise. Even so, by studying the cellular mechanisms that account for the beneficial effects of exercise, it might be possible to develop novel pharmacotherapeutic agents that delay vascular aging by mimicking the effects of exercise (29).

Ungvari and colleagues have provided an important and comprehensive review on vascular aging, which has placed the vascular system center stage for future studies of aging. They have overturned the established concept that aging is an unmodifiable risk factor for vascular disease. This is particularly important given the hypothesis that vascular and microvascular aging is a key mechanism for the aging human phenotype and much of the morbidity and mortality associated with advancing age.

References


