HIGHLIGHTED TOPIC | Physiology of the Aging Vasculature

Arterial aging is risky

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Cardiovascular diseases, i.e., hypertension, coronary heart disease, congestive heart failure, and stroke are the leading causes of morbidity, mortality, and disability in industrialized countries. Epidemiological studies have unequivocally shown that age is the dominant risk factor for these cardiovascular diseases. This cardiovascular disease epidemic is occurring worldwide despite unprecedented advances in the diagnosis and treatment of these conditions, and this situation is only expected to worsen because the world population is aging. Most research efforts to date have focused on developing interventions that target “traditional” risk factors for coronary heart disease (e.g., hypertension, hypercholesterolemia, etc.), whereas little attention has been devoted to aging because age has usually been viewed as an unmodifiable, unpreventable, or untreatable risk factor. This view exposes our major shortcoming in understanding why age is such a potent risk factor for cardiovascular diseases, namely our poor insight into the specific elements that constitute the risky components of aging via the cardiovascular system.

The structure and function of arteries change throughout the lifetime of humans and animals. It is reasonable to hypothesize that specific mechanisms that underlie the arterial substrate that has been altered by an “aging process” are intimately linked to cardiovascular diseases. These changes include lumenal dilation, diffuse intimal and medial thickening, increased stiffness, reduced compliance of central arteries, endothelial dysfunction, and impaired arterial wound repair and angiogenesis. Elucidation of cellular and molecular mechanisms that underlie age-associated alterations in central and peripheral arterial structure and function in health is essential to unravel age-disease interactions and to target the specific characteristics of arterial aging that render it the major risk factor for the aforementioned diseases.

Recent studies reveal a profile of arterial cell and matrix properties that emerge with advancing age within the grossly normal appearing aortic wall of both animals and humans that resembles a proinflammatory state. A “megacept” emerges with the realization that this age-associated profile within the arterial wall is strikingly similar to the inflammatory state that develops in arteries of younger animals in response to experimental induction of early atherosclerosis or hypertension. Thus “aging” and these “diseases” are fundamentally intertwined at the cell and molecular levels. In humans, other well-known risk factors, e.g., altered lipid metabolism, smoking, and lack of exercise, interact with this age-associated proinflammatory arterial substrate, a fertile soil for facilitation of the initiation and progression of arterial diseases.

This Highlighted Topics series, integrating perspectives that range from humans to molecules, briefly reviews selected recent advances in cardiovascular biology that provide insights into the mechanisms that may underlie arterial aging and its increased risks for arterial disease.

The interaction of the arterial system with the left ventricle, termed arterial-ventricular coupling, is a central determinant of cardiovascular performance and cardiac energetics. Chantler et al. (3), provide an overview of the concept of arterial-ventricular coupling, using the arterial elastance (EA)/left ventricular end systolic (ELV) ratio and examine the effects of age, hypertension, and heart failure on EA/ELV and its components (where EA is a measure of the net arterial load exerted on the left ventricle and ELV is a load independent measure of LV chamber performance). In healthy individuals at rest, EA/ELV is maintained within a narrow range, which allows the cardiovascular system to optimize energetic efficiency at the expense of mechanical efficacy. During stress, e.g., exercise, an acute mismatch between the arterial and ventricular systems occurs (due to a disproportionate increase in ELV/EA) to ensure that sufficient cardiac performance is achieved to meet the increased energetic requirements of the body. As a result, EA/ELV decreases from its resting level. Mechanistic insights that can be derived from studying arterial-ventricular coupling are highlighted.

Recent studies have discovered an association between excessive pressure pulsatility due to stiff central arteries and microvascular remodeling and impaired regulation of local blood flow, leading to diffuse microscopic tissue damage and many forms of kidney disease and cognitive impairment. Mitchell (6) summarizes age-related changes in central aortic and peripheral arterial function and discusses potential mechanisms that link age-associated changes in properties of large arteries to excessive pressure pulsatility, abnormal microvascular structure and function, and end-organ dysfunction and damage.

Arterial calcification modifies arterial wall stiffness and may have clinically significant consequences on cardiac function and downstream circulatory control. The calcium content of the arterial wall increases with age. The process and functional consequences of medial elastocalcinoses are reviewed by Atkinson (1).

One of the major conceptual advances in our understanding of the pathogenesis of age-associated cardiovascular diseases has been that age-related oxidative stress may promote arterial inflammation even in the absence of traditional risk factors associated with atherogenesis. Oxidative stress affects the availability and/or balance of key regulators of vascular ho-

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meostosis and favors the accumulation of oxidative damage that impairs arterial function and fosters development of cardiovascular disease. Reactive oxygen species (ROS) are generated by molecular pathways principally located in the cytoplasm and mitochondria. Camici et al. (2) review the role of mitochondrial enzyme p66Shc, an adaptor protein that plays an important role as a redox enzyme implicated in mitochondrial ROS production and the pathophysiology of aging and age-related cardiovascular disease. Csiszar et al. (4) summarize recent experimental data suggesting that mitochondrial production of ROS, innate immunity, the local tumor necrosis factor (TNF-α) converting enzyme (TACE)-TNF-α, and the renin-angiotensin system underlie nuclear factor-κB (NF-κB) induction and endothelial activation in aged arteries. The convergence of these diverse proinflammatory pathways on NF-κB in the aged arterial wall regulates NF-κB transcriptional activity via multiple nuclear factors, including the nuclear enzymes PARP-1 and SIRT-1. The possibility that nucleophosmin (NPM or nuclear phosphoprotein B23), a known modulator of the cellular oxidative stress response, may regulate NF-κB activity in endothelial cells also is discussed.

An increase in ROS production and a decrease in nitric oxide (NO) bioavailability contribute to vascular endothelial dysfunction with aging. Santhanam et al. (7) review how an age-associated increase in the activation/upregulation of arginase contributes to age-related endothelial dysfunction by a mechanism that involves substrate (L-arginine) limitation for endothelial NO synthase (NOS3) and, therefore, NO synthesis. Not only does this lead to impaired NO production, but contributes to the enhanced production of ROS by NOS3. Furthermore, arginase activation may contribute to aging-related vascular changes by mechanisms that are not directly related to changes in NO signaling, e.g., vascular smooth muscle proliferation and collagen synthesis.

Angiogenesis and arterial wound repair require proliferation and differentiation of endothelial precursor cells and subsequent proliferation and migration of endothelial cells. In most somatic mammalian cell types, extensive replication and various types of cellular insults induce a permanent form of growth arrest called senescence. Recent evidence indicates that populations of cells within the aged arterial wall exhibit features of cell senescence.

Therapies that reduce or retard this age-associated proinflammatory state within the arterial wall may have a substantial impact on development of arterial diseases. There also are indications that, as with other cardiovascular risk factors, lifestyle modifications including aerobic exercise and dietary modifications (e.g., reduction in NaCl intake, caloric restriction, weight loss) can prevent or retard intimal-medial thickening, arterial stiffening, and endothelial dysfunction with aging. Seals et al. (8) review evidence that habitual physical activity/increased aerobic exercise capacity favorably modulates some aspects of arterial aging and likely improves the ability of aged arteries to cope with arterial disease burden. Compared with their sedentary peers, adults who regularly perform aerobic exercise demonstrate smaller or no age-associated increases in large elastic artery stiffness, reductions in vascular endothelial function, and increases in femoral artery intimal-medial thickness. A short-term, moderate-intensity aerobic exercise intervention (brisk daily walking for 12 wk) improves carotid artery compliance and can restore vascular endothelial function in previously sedentary middle-aged and older adults. These effects may be linked to a reduction in oxidative stress.

In summary, a host of biochemical, enzymatic, and cellular alterations that operate to accelerate arterial aging also have been implicated in the pathogenesis and progression of arterial diseases. These age-associated alterations impair arterial regulatory mechanisms and the ability of arteries to adapt, repair, and remodel through the integration of multiple signaling mechanisms. A failure of this plasticity of the arterial wall with aging ultimately governs the macroscopic structural and mechanical properties of arteries with advancing age and disease. These cellular/molecular alterations are thus novel putative candidates that could be targeted by interventions aimed at attenuating arterial aging, similar to the lifestyle and pharmacological interventions that have already been proven effective.

REFERENCES