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Arteriosclerosis: a primer for "In Focus" reviews on arterial stiffness

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Arteriosclerosis, a descriptive term for thickening and hardening of the arterial wall, accompanies aging and is associated with major adverse impact on the cardiovascular system and a number of other diseases that are now known to have a strong underlying microvascular component to their pathogenesis, including chronic kidney disease, vascular dementia and Alzheimer disease.[1;2] Although a multitude of studies have attempted to identify genetic contributions to arterial stiffening in humans, the results have been largely inconclusive, in part due to lack of appreciation of both the population epidemiology of arterial stiffness and the variety of measurement methods and arterial beds used to assess arterial stiffness.[3] Recently, two separate groups have capitalized on the UK Biobank study to report genome wide association studies of finger plethysmography measurements of arterial stiffness index, with emerging indications that collagen gene *COL4A2* variants may be associated with arterial stiffness index.[4;5] However, finger plethysmography does not provide a robust measure of the stiffness of the central elastic arteries, which is of critical importance to cardiac function. Progress in the pathobiology of arterial stiffness depends on designing experimental studies which consider the challenges posed by the epidemiology and measurement of arterial stiffness. Therefore, the purpose of the forthcoming series of "In Focus" reviews is to identify these challenges for vascular biologists together with their clinical and genetic colleagues.

Arterial stiffness or arteriosclerosis is often associated with but is distinct from atherosclerosis, which is a patchy intimal abnormality that likely represents a consequence rather than a cause of arteriosclerosis.[6;7] Arteriosclerosis arises as a result of increased production or progressively greater engagement of stiffer load bearing elements in the arterial wall, such as collagen. Stiffening of the aorta increases pulsatile load on the left ventricle, leading to hypertrophy and diastolic dysfunction, which can progress to heart failure, often with preserved left ventricular ejection fraction.[8–10] Aortic stiffening reduces the normal impedance gradient between aorta and branching conduits and thereby increases pulsatile pressure and flow in downstream conduits, such as the carotid and renal arteries, leading to transmission of excessive pulsatility into the fragile microcirculation, particularly in high-flow organs such as the brain and kidneys.[11–13] In these low impedance vascular beds, low precapillary resistance allows excessive pulsatile energy that enters the local conduit artery to be transmitted directly into the microcirculation, where it causes

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microvascular damage, remodeling and repair, leading to target organ damage and dysfunction.

Risk factors for arterial stiffening other than age and distending pressure remain relatively obscure.[6] Though once thought to represent a consequence of longstanding hypertension, it is now clear that aortic stiffening precedes and contributes to the pathogenesis of hypertension.[14] Arteriosclerosis arises in part as a consequence of a lifelong progressive increase in aortic diameter, which accommodates an increase in cardiac output associated with normal somatic growth in early life and progressive pathologic obesity from adulthood onward.[15] While aortic remodeling maintains the balance between flow and diameter, it may accelerate deterioration of elastic elements in the aortic wall. The complement of medial elastic fibers in the aortic wall is determined by a complex interplay of genetic and environmental factors and is completed early in life at the equivalent of the toddler stage in various animal models and humans. The complex gene program that is required to produce medial elastic fibers is subsequently silenced,[16;17] resulting in a fixed complement of elastic fibers that must last a lifetime.[18]

Progressive remodeling to a larger diameter of this fixed pool of elastic fibers in the aortic media leads to thinning and increased elastic fiber stress and transfers progressively greater load bearing to much stiffer collagen fibers. As the wall stiffens, pulse wave velocity increases. Remodeling to a larger diameter can limit the increase in pulse pressure (the difference between systolic and diastolic pressure) associated with a given increase in wall stiffness because characteristic impedance of the aorta (Zc), which defines the change in pressure (dP) produced by a given change in flow (dQ) in the aorta (Zc = dP/dQ), has a strong inverse association with lumen diameter. However, progressive stiffening eventually overwhelms diameter remodeling at around midlife, leading to a progressive increase in systolic and pulse pressure thereafter, particularly in women.[15;19] The increase in pulse pressure plays a major role in the pathogenesis of isolated or predominant systolic hypertension, which is highly prevalent after midlife and is often difficult to control adequately.[20]

The combination of high risk associated with aortic arteriosclerosis plus the epidemic prevalence of increased stiffness in middle-aged and older people implies that the burden of disease attributable to stiffness will rise considerably over the next two decades as the population ages if we do not find ways to prevent or reverse excessive stiffness.[21;22] While age-related stiffening is highly prevalent, it is not inevitable, underscoring the need for additional research on pathogenesis and vascular biology of stiffening and factors that promote healthy vascular aging.[23]

In this context, ATVB has commissioned a series of brief reviews that aims to underscore the critical importance of aortic arteriosclerosis in the pathogenesis of cardiovascular disease while outlining what we know and what we need to better understand about pathogenesis and consequences of arteriosclerosis. Wilkinson et al. present arterial stiffness in the clinical context, while Yu and McEniery present a brief review of the epidemiology of stiffness. Schutte et al. provide an overview of ethnic differences in aortic stiffness. Segers et al. describe various techniques that have been developed to assess arteriosclerosis in humans

while Butlin et al. address the unique challenges of performing stiffness measurements in small animals. Laurent et al. summarize current understanding of various factors, including smooth muscle cell biology, that contribute to stiffening of the arterial wall while Chen et al. look specifically at factors associated with arterial calcification.

We trust that this series of reviews will stimulate high-quality aspirational research that aims to elucidate factors that contribute to arterial stiffening, its consequences and reversal.

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