The Pressure of Aging

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KEYWORDS

- Hemodynamics • Aging • Arterial wall remodeling
- Age-dependent salt-sensitive hypertension • Pulse wave velocity • Arterial fibrosis
- Angiotensin II • Marinobufagenin

KEY POINTS

- Although preclinical hemodynamic alterations observed early in life are not directly harmful, they form the basis for the deleterious hemodynamic effects observed with aging.
- The aortic biomechanics underlie the increase of salt sensitivity with advancing age, and a novel pro-fibrotic marker, an endogenous sodium pump ligand, marinobufagenin links aging, salt sensitivity, and arterial stiffness.
- A proinflammatory state in the arterial wall, with a pivotal role for angiotensin II (Ang II), is a key component of arterial aging.
- Pulsatile damage to the arterial wall and the proinflammatory state within the arterial wall interact in a vicious cycle, resulting in increasing arterial wall fibrosis.
- Therapies to prevent or delay Ang II signaling–related vascular changes that accompany aging to ultimately reduce the prevalence of hypertension should be aimed at breaking the vicious cycle at its early stages.

INTRODUCTION

Major hemodynamic alterations ensue with aging and are primarily attributable to central arterial stiffening[1]; these alterations become manifest in the ever-expanding epidemic of hypertension affecting 1 of every 3 Americans in general and a staggering rate of 7 of every 10 of those aged 65 years and older.[2] The burden of this epidemic is projected to increase with the aging of our population as the percentage of people aged 65 years and older increasing from 15% in 2014 to 22% in 2030.[3] This shift in demographics makes predominantly systolic hypertension, a challenging form of hypertension that becomes more prevalent with advancing age and that dominates the

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Med Clin N Am 101 (2017) 81–101
http://dx.doi.org/10.1016/j.mcna.2016.08.006 **medical.theclinics.com**
0025-7125/17/Published by Elsevier Inc.

hypertension field.[4] All of these factors make hypertension a growing health burden with predicted hypertension-related health care costs reaching $389 billion in 2030.[5] Because aging is the major risk factor for predominantly systolic hypertension, the pivotal question to effectively address this hypertension epidemic is the following: What underlies arterial aging?

Evolutionary biologists proclaim that most of us are wired to be very healthy until around the end of childbearing age, because the main reason for our reality, they would say, is to perpetually insure the next generation of our species; after that, from an evolutionary perspective, there is no essential reason for us to be alive. However, we do remain alive longer well beyond our evolutionary life expectancy prescription because our environment has been enhanced by improved hygiene, better nutrition, better health care, and so forth. But, in outliving our Paleolithic gene set, disorder among molecules within our body progressively increases and functional declines accumulate with advancing age; beyond 40 years we become vulnerable to what are referred to as "degenerative chronic diseases of aging." Arterial aging and the associated alteration in hemodynamics are no exception.

The hypertension field has been struggling to better understand the complex relationship between arterial wall mechanical changes (ie, arterial wall stiffness) and hemodynamics (ie, arterial pressure alterations) and has been fixated on defining which factor is the culprit. The failure to reach an unequivocal answer is not surprising and is probably a reflection of the naivety of the question. In health homeostasis, a functional crosstalk between central and peripheral segments of the circulation is required for optimal operation. Once this homeostasis is broken, for any reason, a vicious cycle of minute alterations in central arterial mechanical and hemodynamics ensues and propagates, leading to the dramatic changes in arterial properties observed with aging. Thus, in this paradigm, it is close to impossible to detect the initial minute alteration and point to it as the culprit.

Given this extreme complexity, any efforts directed at treating or preventing the increase in blood pressure would be infertile without major efforts being committed to further explore the underpinning aging of the arterial wall. These efforts should be aimed at revealing early alterations, starting in young adulthood, before reaching the clinical threshold and developing stage/process-specific interventions rather than the one-size-fits-all approach that dominates hypertension. In the meantime, targeting elements of this vicious cycle, the master perpetuators of arterial aging, seems to be the most promising strategy to reduce the health burden of hypertension.

AGE-ASSOCIATED DYSFUNCTION OF CENTRAL ARTERIES AND HEMODYNAMIC ALTERATIONS

Epidemiologic studies have pursued the description of changes in arterial stiffness with aging and to answer the question of whether central arterial stiffness is a cause or an effect of elevated systolic and pulse blood pressure. One of the difficulties in addressing this issue relates to a degree of ambiguity and restrictions of the terms *blood pressure* and *arterial stiffness*. This question might be better articulated if we expand these terms and rename *arterial stiffness* as *arterial mechanical alterations* and *elevated blood pressure* as *hemodynamic alterations*; then, it becomes apparent that arterial mechanical properties and hemodynamics are inseparable and the question on what starts first, mechanical or hemodynamic alterations, seems to be somewhat naïve.