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The Conundrum of Arterial Stiffness, Elevated Blood Pressure, and Aging

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Abstract Isolated systolic hypertension is a major health burden that is expanding with the aging of our population. There is evidence that central arterial stiffness contributes to the rise in systolic blood pressure (SBP); at the same time, central arterial stiffening is accelerated in patients with increased SBP. This bidirectional relationship created a controversy in the field on whether arterial stiffness leads to hypertension or vice versa. Given the profound interdependency of arterial stiffness and blood pressure, this question seems intrinsically challenging, or probably naïve. The aorta's function of dampening the pulsatile flow generated by the left ventricle is optimal within a physiological range of distending pressure that secures the required distal flow, keeps the aorta in an optimal mechanical conformation, and minimizes cardiac work. This homeostasis is disturbed by age-associated, minute alterations in aortic hemodynamic and mechanical properties that induce short- and long-term alterations in each other. Hence, it is impossible to detect an "initial insult" at an epidemiological level. Earlier manifestations of these alterations are observed in young adulthood with a sharp decline in aortic strain and distensibility accompanied by an increase in diastolic blood pressure. Subsequently, aortic mechanical reserve is exhausted, and aortic remodeling with wall stiffening and dilatation ensue. These two phenomena affect pulse pressure in opposite directions and different magnitudes. With early remodeling, there is an increase in pulse pressure, due to the dominance of arterial wall stiffness, which in turn accelerates aortic wall stiffness and dilation. With advanced remodeling, which appears to be greater in men, the effect of diameter becomes more pronounced and partially offsets the effect of wall stiffness leading to plateauing in pulse pressure in men and slower increase in pulse pressure (PP) than that of wall stiffness in women. The complex nature of the hemodynamic changes with aging makes the "one-size-fits-all" approach suboptimal and urges for therapies that address the vascular profile that underlies a given blood pressure, rather than the blood pressure values themselves.

Keywords Aging · Hypertension · Pulse wave velocity · Aortic diameter · Aortic remodeling

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Introduction

Hypertension is an escalating major global health problem with eight out of ten people are likely to have hypertension in their lifetime [1]. It affects more than 40 % of the world's population aged 25 and older, and nearly 80 % of people aged 75 and older; it is responsible for about 13 % of the total of all deaths worldwide [2]. The direct and indirect costs of hypertension in the USA are estimated at US$46 billion and are projected to increase to US$274 billion by 2030 [3]. Despite the great efforts to control hypertension, the number of subjects with uncontrolled hypertension increased from 800 million in 1988 to nearly 1 billion in 2008 [2]. This increase is mainly due to the aging of our population with the percentage of the people aged 65 and older rising, from 5 % in 1950 to

8 % in 2010, with a projected increase to 16 % in 2050, accounting for 1.5 billion people [4]. This implies a vast expansion of an already costly and fatal epidemic of hypertension in the next few decades that warrants great efforts to prevent and treat this condition.

A deeper understanding of the pathophysiology that underlies hypertension is essential for any breakthrough in this direction. The mainstay approach to control blood pressure is to target mean blood pressure (MBP) by affecting heart rate, stroke volume, and peripheral vascular resistance; this approach is ineffective, if not harmful, when the issue is actually an elevation in pulse pressure (PP) rather than MBP [5]. This is the case in isolated systolic hypertension (ISH), the dominant form of hypertension in both young and old individuals with exponentially increasing dominance with advancing age [6, 7].

While central arterial stiffness with aging is strongly implicated in the pathogenesis of ISH, controversy exists regarding the direction and nature of this relationship, with evidence supporting a role of arterial stiffness in the initiation and progression of ISH, and vice versa. Here, we aim to elucidate the conundrum of arterial stiffness, elevated blood pressure and aging by reviewing the physiological function of the aorta, and the epidemiological evidence of age-associated alterations in aortic properties and blood pressure parameters.

The "Purpose" of the Aorta: an Evolutionary Perspective

In early stages of life, eukaryotes evolved in physically stationary, chemically renewable, microenvironments. The evolution of multicellular organisms with increasing complexity required solving the problem of maintaining the characteristics of microenvironments for the individual cells that are mostly not in direct contact with the external environment. This was an easier task in early forms of multicellular organisms such as the hydra, with a cylindrical body consisting of two-cell-thick wall enclaving a gastrovascular cavity connected with the external world; the peduncle of the hydra provides random contraction "beats" shaking the intracavitary fluid, while the epithelial flagellated cells simply move the fluids around [8].

A dedicated circulatory system evolved with the evolution of more complex organisms in which internal and external environments are separated by an epithelium. While the heart generates pulsatile flow, it is the aorta that receives this pulsation and, via a Windkessel effect, dampens it into an almost continuous distal flow securing a physically stable environment for cells in the periphery [9]. The aorta provides elasticity over a physiological perfusing pressure range of a given organism in order to achieve dampening of pulsatility in the physiological pressure range and tensile strength to contain the stroke volume and avoid rupture at higher pressure.

Having aortae composed of fibrillin microfibers, along with other extra-cellular matrix components, such as collagen, provided the elasticity required to minimize pulsatility in animal with low-pressurized, open circulation [10]. The appearance of vertebrates, however, with a closed circulation resulted in increased peripheral resistance and higher mean arterial pressure [11]. Since the fibrillin microfibrils alone become very stiff in the context of newly evolved organisms requiring higher perfusion pressure, an increase in pulsatility might have imposed a selection pressure for the evolution of another extra-cellular matrix element required to provide elasticity at higher pressures; this element is tropoelastin [10]. In contrary to other ECM components, tropoelastin evolution coincided with the evolution of the highly pressurized systems indicating its critical role in modulating pulsatile hemodynamics in the newly evolved blood pressure range.

The Cross-Talk Between the Heart, the Aorta, and the Peripheral Circulation

The evolution of elastin is an example of cardiac-aortic-peripheral arterial cross-talk at an evolutionary level; the peripheral modification accompanying the evolution of the closed circulation required a central arterial modification to adapt to/optimize the new peripheral hemodynamics, while maintaining optimal cardiac work.

Similar to many phylogenic evolutionary phenomena, ontogenic cross-talk between the different components of the vascular bed is recapitulated in fetal development; the shift from low pressurized to high pressurized circulation due to peripheral changes around birth triggers the production of elastin in central arteries [10]. This cross-talk represents a complex control circuit including cardiac output, elastin-collagen recruitment, vascular smooth muscle tone, and endothelial function, to count few. This control circuit assures optimal distal flow, arterial wall stress, and cardiac loading in different physiological states, i.e., exercise and pregnancy. One limitation in this control circuit is the non-renewable status of elastin, which is only produced around birth and goes through slow turnover with aging [12]. This, along with additional alterations to other components of the circuit that might arise with aging, converts this elegant control circuit into a vicious cycle of drastic hemodynamic alteration. Hence, age-associated alterations to the structure and function of elastin are implicated in the increased central pulsatility that accompanies advancing age. These alterations are associated with activation of a proinflammatory profile leading to

fibrotic and calcification processes leading to further increase in arterial wall stiffness (Fig. 1).

Age-Associated Changes in Aortic Properties and Blood Pressure in Humans

Epidemiological studies have been pursued to describe 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 in these terms. 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 bears apparent that arterial mechanical properties and hemodynamics are inseparable and the question on what starts first, mechanical or hemodynamic alterations, appears to be somewhat naïve.

In the Beginning… Early Alterations of Arterial Mechanics and the Rise in Diastolic Blood Pressure with Aging

The initial evidence of age-associated arterial mechanical alterations is observed by the third decade of age with sharp declines in aortic strain, the difference between aortic systolic and diastolic diameters relative to the diastolic diameter, and in aortic distensibility, i.e., aortic strain divided by pulse pressure; analysis of cardiac magnetic resonance (CMR) imaging of 111 healthy participants has shown that nearly 80 % of the total decline of aortic strain occurs before the fifth decade of age after which the decline in strain is less dramatic [13] (Fig. 2a); however, the small decline in aortic strain beyond

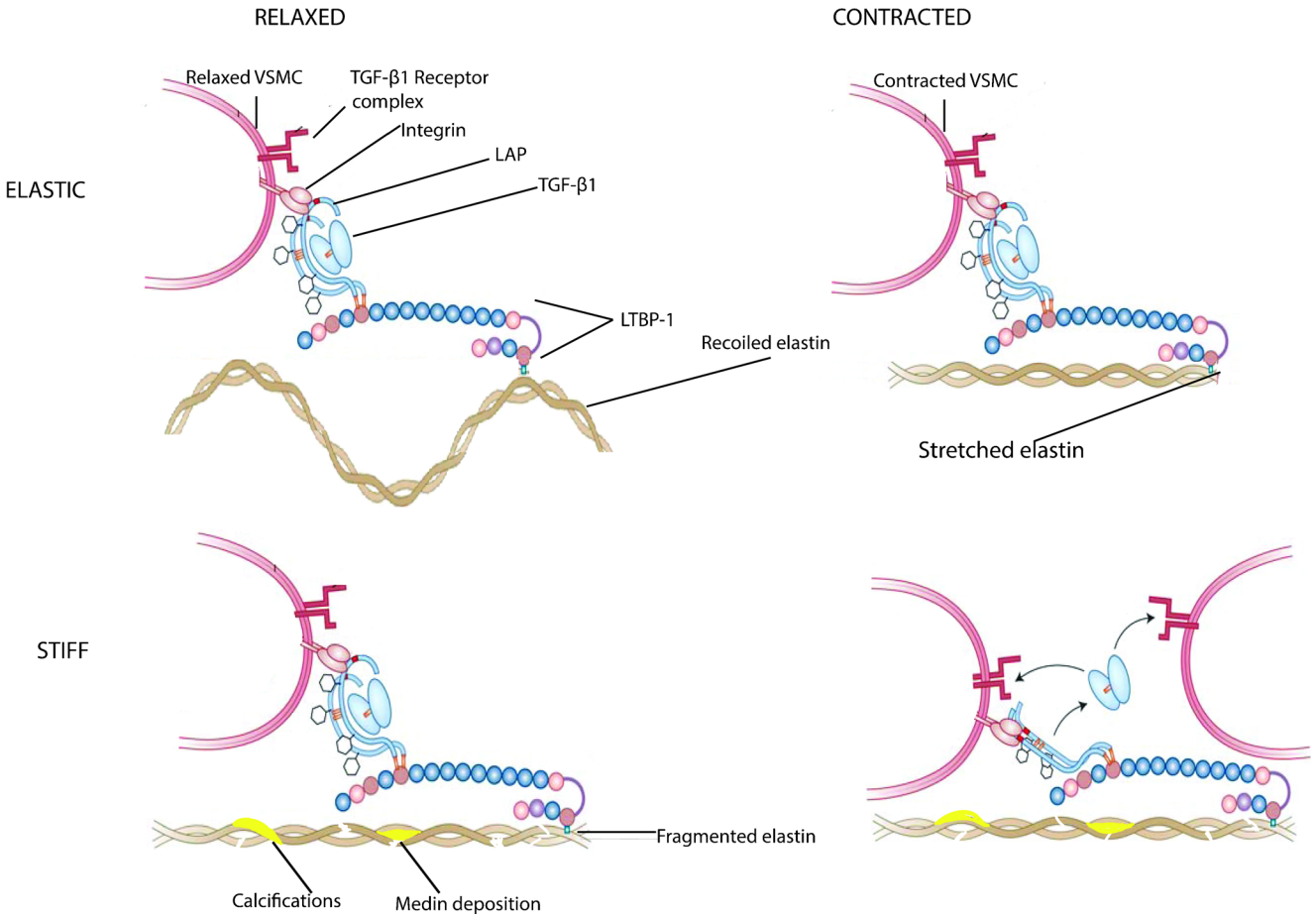

Fig. 1 A schematic model illustrating the mechanism of TGF-β1 activation with loss of elasticity. TGF-β1 is secreted in a large latent complex, consisting of TGF-β1 associated with the latency associated peptide (*LAP*) and the latent TGF-β1-binding protein (*LTBP-1*). This structure links VSMCs to elastic fibers. In normal-functioning elastic arteries, VSMC contraction pulls the whole compound with the elastic fiber connected to it. With the loss of elasticity, calcification, amyloidization, and other factors, the elastic fiber is less mobile and traction forces exerted by the stiffer VSMCs is transferred to LAP potentially resulting in activation of TGF-β1 and subsequent fibrosis (adapted from [36])

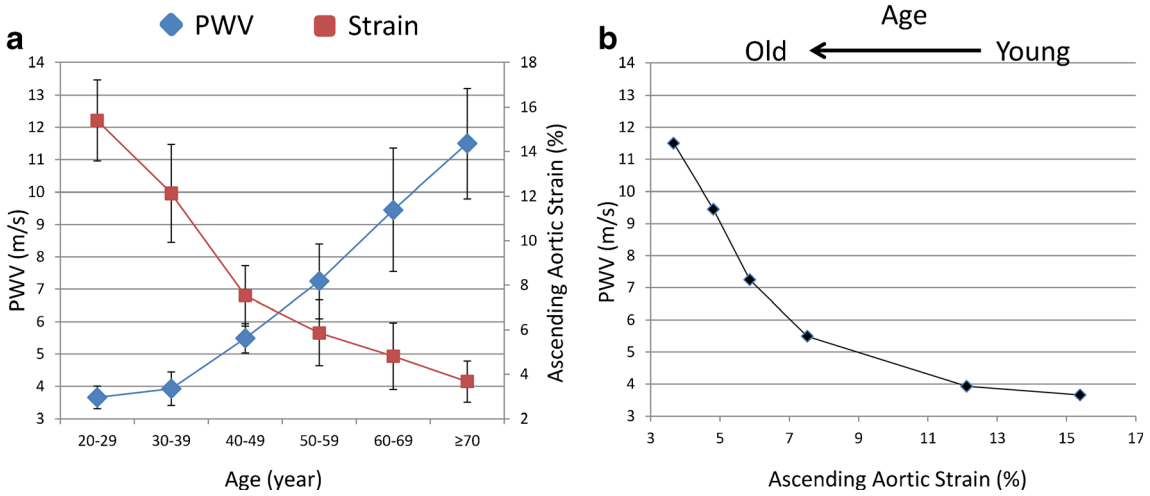

Fig. 2 Early age-related changes in aortic distensibility precede the changes in PWV. **a** Aortic strain (*red*) decreases sharply between the third and fifth decades of life after which there is a sharp rise in aortic pulse wave velocity (*blue*). **b** Aortic strain and PWV plotted against each other showing an exponential increase in PWV with declining aortic strain with aging (modified from [13])

the age of 50 was associated with an exponential increase in pulse wave velocity (PWV) with aging (Fig. 2b). Preliminary analyses that further examine the decline in arterial strain and distensibility in the SardiNIA project, a large cohort study of 6000 community-dwelling participant from Sardinia, Italy, have shown that the earlier decline in common carotid arterial strain and distensibility is not associated with a decreased "restricted" systolic diameter, but rather with an increase in diastolic diameter, independent of changes in distending blood pressure [14]. This later phenomena is consistent with an initial impaired diastolic recoil and not a restrictive process, commonly inferred from the notion that increased fibrosis and calcification are among the main stiffening processes.

During the same stages of life, as central arterial strain is becoming reduced, there is an increase in diastolic blood pressure [5, 15••], which could be associated with progression of increased endothelial dysfunction with aging, leading to increased peripheral vascular resistance. While such changes are not very well studied in normal human subjects, those with essential hypertension demonstrate eutrophic, inward remodeling of small arteries [16, 17]. It is not clear whether the increase in diastolic alters the optimal conformation of the arterial wall making it prone to increased hemodynamic stress and to additional mechanical alterations beyond those resulting from simply stretching elastin fibers at higher pressures and shifting the load to the stiffer collagen fibers.

Beyond the fifth Decade of Age: Central Arterial Mechanics and the Pulsatile Hemodynamic

Dramatic hemodynamic alterations ensue beyond the fifth decade of life, as increases in systolic blood pressure (SBP) and PP become the hallmarks of arterial aging [5]. Major histological and subsequent mechanical alterations in the central arterial wall are observed at this stage. These are characterized by a proinflammatory profile, metabolic stress, elastin fragmentation and calcification, collagen deposition, and vascular smooth muscle cell (VSMC) stiffness [18], reduced responsiveness to vasodilators, and increased proliferation and migration [19] (Fig. 3); among these factors, the effects of changes in elastin [20] and central arterial VSMC stiffness [20–22] on arterial wall stiffness are more pronounced. These changes result in mechanical alterations that manifest in a dramatic increase in PWV, the best currently available measurement of arterial stiffness.

An experimental animal model has shown that an increase in PWV occurs without any increase in blood pressure in non-human primates fed with diet high in fat and sucrose [23]. Similarly, Dahl salt-sensitive hypertensive rats develop an increase in PWV that precedes the increase in blood pressure in response to salt loading [24]. Although these experimental animal models did not address the issue of aging, however, in reality, they do support the notion that the increase in PWV occurs independent of pressure changes.

PWV and blood pressure parameters have been shown to be strongly associated in cross-sectional and prospective studies [25, 26]. A study of 483 participants evaluated at two visits about 6 years apart has shown that subjects with uncontrolled hypertension have greater increase in PWV compared to those with normal blood pressure or those with controlled hypertension [27]. Data from the Caerphilly Prospective Study have shown that the cumulative effect of PP and HR also predicts PWV at 20 years; however, unfortunately, this study did not have baseline PWV limiting the interpretation of these results [28•]. On the other hand, in a prospective study of 259 subjects who underwent repeated follow-up for 16 years, PWV increase over time was observed independent of changes in mean arterial pressure due to treatment [29]; it is worth noting in this

Fig. 3 Conceptual model of arterial aging. Age-associated cellular disorders and cumulative mechanical stress lead to a state of chronic inflammation, elastin degradation, and endothelial and VSMC dysfunction. These processes interact and lead to arterial wall calcification, fibrosis, amyloid deposition, VSMCs proliferation, and increased intimal medial thickness. These structural changes lead to functional alterations resulting in widened pulse pressure (adapted from [36])

study that those with AGTR1 genotype 1166C was associated with greater increase in PWV, independent of blood pressure or antihypertensive treatment after the age of 55 [29].

The Framingham Heart Study, using data from cycle 7 to predict SBP and PWV in cycle 8, has shown that higher PWV in cycle 7 was associated with higher SBP in cycle 8 [30•]; however, the opposite was not true that SBP at cycle 7 was not associated with higher PWV in cycle 8. It is noteworthy, however, that one of the shortcomings of such design with a relatively short follow-up time of 7 years is that it does not address that the magnitude and the direction of association between SBP and PWV could change with aging and differ by gender; merely adjusting for these variables does not inform whether these associations differed between the different categories of these variables. Hence, the findings reflect the average associations over the age spectrum studied for both genders.

New Longitudinal Perspective on the Conundrum of Arterial Wall Stiffness, Blood Pressure, and Aging: a Vicious Cycle Between Teammates that Eventually Diverge

Indications of a Vicious Cycle Between Arterial Stiffness and Systolic Blood Pressure

The Baltimore Longitudinal Study of Aging (BLSA) is a cohort study of community-swelling populations with extended follow-up time (1988–2013) and multiple repeated measures of PWV and BP. Earlier analyses from the BLSA have shown that greater PWV was associated with larger increase in SBP with aging and predicted the incidence of hypertension [31•]. Recent analysis from the BLSA, however, using linear mixed-effects models, shed light on the vicious cycle, showing that higher SBP, in a dose-dependent fashion, is associated also with a greater rate of increase in PWV over time; this association was more pronounced in men with accelerating rates of increase in PWV at higher SBP with advancing age [32••].

Dissociation Between PWV and SBP Trajectories: When the Teammates Diverge

New insight on the longitudinal changes in PWV and SBP parameters came from the SardiNIA data with examination of the concurrent trajectories of repeated measures of PWV and SBP; using linear mixed-effects models allows the examination of whether the longitudinal changes of these parameters over time vary by starting age [15••]. This analysis demonstrated a striking dissociation in the trajectories of these parameters with advancing age, a dissociation more pronounced in men than in women [15••]. Figure 4 illustrates the cross-sectional differences "beginning of the splines" and the longitudinal changes (slopes of the splines) with aging (rates of changes are illustrated in the lower panels) of PWV and SBP in both men and women. In men (Fig. 4 left panels), PWV increased with age at rates that increase linearly with advancing age; however,

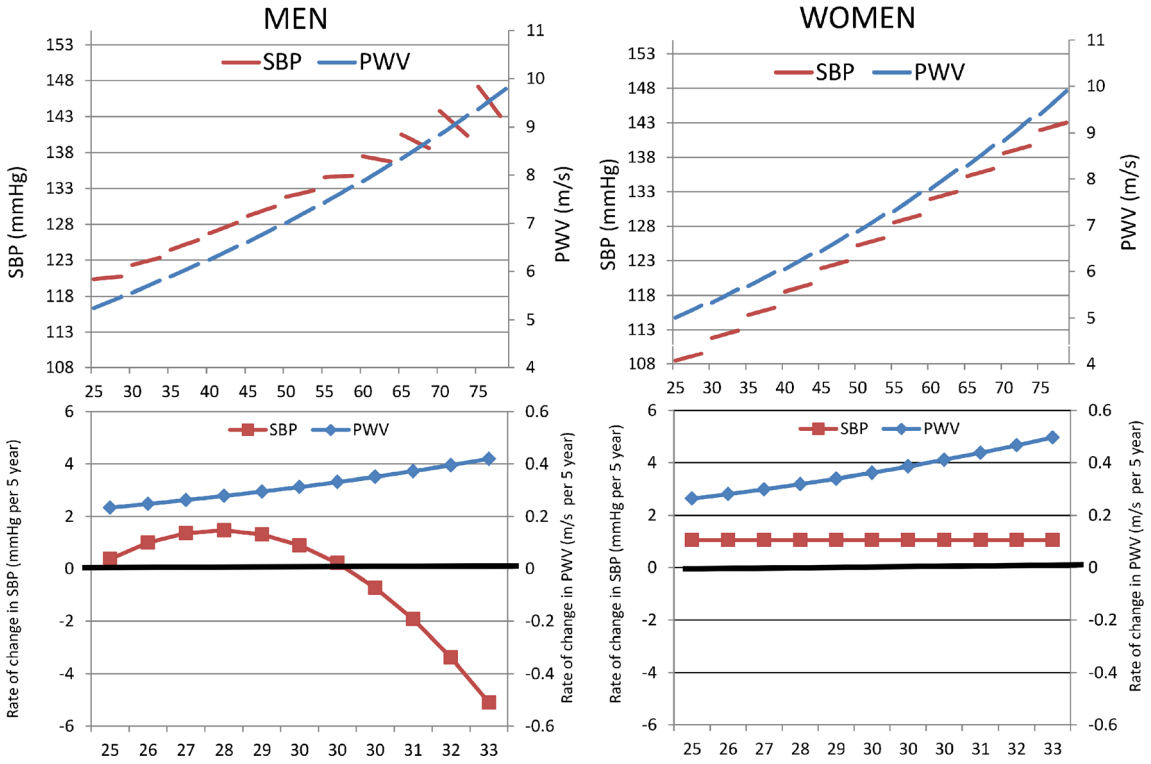

Fig. 4 Linear mixed-effects models predicted PWV and SBP values illustrating gender-specific cross-sectional differences "beginning of the splines" and the longitudinal changes (slopes of the splines) with aging (rates of changes are illustrated in the *lower panels*) in men and women from the SardiNIA project (adapted with modification from [15])

although cross-sectional SBP continues to increase, the longitudinal rates of change, while initially increasing, begin to decline with time; thus, the rates of change in SBP diverge from those of PWV by the fifth decade. A similar, but a less dramatic, divergence is observed in women (Fig. 4 right panels); while PWV showed the same pattern of longitudinal changes in men with linearly increasing rates of change with advancing age, SBP increased longitudinally at a steady, rather than increasing, rates throughout the age range studied. Of note, the longitudinal associations between changes in PWV and SBP, which would have demonstrated the vicious cycle, were not evident in the SardiNIA study in part due to the conservative statistical approach that was implemented. Preliminary analyses from the BLSA using the same approach of examining the concurrent trajectories showed a similar pattern of dissociations between PWV trajectories and those of SBP and PP, which were more pronounced in men than in women [32••].

Epidemiological Insight into the Discrepancy Between the SardiNIA and BLSA Findings and the Established Views on SBP Increase with Aging

The longitudinal plateauing and then decrease in SBP among men with advancing age found in the SardiNIA [15••] and the BLSA data (preliminary analysis) [33] seem to contradict the conventional wisdom of an ongoing increase in SBP with aging; this apparent contradiction brings the attention to the impact of the analytical approaches to longitudinal data on the results that one would get. First, a pronounced limitation of any epidemiological study aimed at examining the trajectories of a parameter, SBP in this case, over a broad age range is that it is close to impossible to have a cohort that enters the study at the same young age and then to be followed all the way to an advanced age. Hence, large epidemiological studies implement a design in which participants enter studies at different ages and then be followed for a specific time; then, the whole data is analyzed to produce the trajectories over a wide age range by compiling the trajectories of the different "sub-cohorts" studied. The main reason for constructing longitudinal data is to avoid the selection biases that are implicated in cross-sectional studies, especially at older age where those who are enrolled have SBP that are usually consistent with a survival/functional status advantage. This fact is often overlooked, and, when constructing these trajectories, the average values of a blood pressures at a given age are derived from all participants, those who were just enrolled at that age and those who enrolled earlier and has been followed up tell that age. Hence, any

longitudinal changes could be contaminated with the cross-sectional differences and the established trajectories would represent the average of these two forces.

The analytical approach implemented in analyzing the SardiNIA and the BLSA data using linear mixed-effects models with age expressed as entry age "cross-sectional differences" and follow-up time "longitudinal changes", allows separate assessments of the age-related cross-sectional differences and longitudinal changes of SBP, and beyond that to assess whether the longitudinal changes vary with age. This approach allows the revelation of "pure" longitudinal changes in the studied cohort, while showing the age-related cross-sectional differences. A study that attempted reconstructing the life course trajectory of SBP using series of eight different longitudinal cohorts that each covered a segment of human life span showed similar results to that shown in the SardiNIA and the BLSA supporting this explanation [34]. In addition, if the SardiNIA data, for example, is reanalyzed ignoring the cross-sectional differences and focusing on the follow-up SBP values alone (the end point of the splines in the upper panels of Fig. 4), the results show slowing of SBP increase, rather than a decline, which is almost identical to those from the Framingham Heart Study, in which the cross-sectional differences and the longitudinal changes in SBP were averages. The facts that the steeper rate of decline in SBP was not monotonic but was accentuated with advancing age, was different by gender, and was independent of antihypertensive treatment and that it was associated with an escalating rates of increase in PWV, all make it unlikely to be a manifestation of regression to the mean, first-visit white coat effect, or secular changes, although one cannot totally exclude such effects.

A potential Physiological Explanation for the Dissociation Between PWV and the Decline in SBP with Aging in Men

Dissociations between the rates at which PWV and SBP change over time bring our attention again to terminology; "arterial stiffness" usually implies an increase in arterial opposition to flow, i.e., characteristic (Z_c) impedance. However, Z_c, per the water hammer equation is a function of both PWV and aortic diameter squared [35]. Hence, an explanation for the dissociation between SBP and PWV longitudinal trajectories in men is an increase in aortic diameter. Preliminary analysis from the BLSA shows a greater increase in aortic root dilatation with increasing age in men than in women [36]. The net effect of increasing PWV and aortic diameter approximated by applying the water hammer equation is, in fact, a less pronounced increase in calculated Z_c in men despite their more pronounced increase in PWV which was offset by the greater increase in diameter [36]. While these might explain how PWV and SBP/PP trajectories would diverge, the role of wave reflection in this dissociation is not well clear and it is worth further examination.

Summary

The hypertension field has been struggling to better understand the complex relationship between arterial mechanical and hemodynamic alterations and fixated on answering the question: "which 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 cross-talk 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 starts 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."

However, the data discussed above suggest that the vicious cycle evolves into different stages the hemodynamic and mechanical patterns of which depends on the net effect of multiple factors that are interdependent and changes at different rates and directions with aging over a lifetime. In early adulthood, the heart, the aorta, and the peripheral circulation system form an "optimal" setup; the perfusing pressure needed puts the aorta in an optimal conformation for best Windkessel effect that in turn provides optimal pulsatility of the system. In the first phase of the vicious cycle, there are early alterations in arterial strain and distensibility associated with a rise in diastolic and mean blood pressure. By the fifth decade, arterial strain and distensibility reach a nadir while diastolic and mean blood pressures reach a peak and start a downward trend; these changes lag about a decade in women than in men. In the second phase, aortic structural remodeling is more pronounced with an increase in arterial wall stiffness and aortic dilatation; remodeling progresses at a greater rate in men than in women with a more pronounced dilatation and an increase in wall stiffness. Since the main manifestations of aortic remodeling, i.e., wall stiffness and lumen dilatation, affect aortic characteristic impedance, a major determinant of pulsatility, in opposite directions and at different rates, the net effect of these changes would vary across the age spectrum. Initially, they result in increased impedance and widening pulse pressure, which interplay with wall stiffness and lumen dilatation in a vicious cycle. Finally, given the greater increase in arterial stiffness and wall dilatation in men than in women and that diameter imposes a stronger effect on impedance,

the increase in pulse pressure observed in the previous phase is attenuated in men as result of a decline in SBP that parallels the ongoing decline in DBP, leading to a plateau in PP. In women, on the other hand, the lower rate of remodeling slows the increase in SBP but does not result in a decline like the case in men; with DBP continuing to drop, pulse pressure continues to increase with age.

Given this extreme complexity, any efforts directed to treating or preventing the increase in blood pressure would be infertile until major efforts are committed to further explore the underpinning pathophysiology of this complex relationship, starting in young adulthood, before these alterations reach the clinical threshold, and to develop stage/process-specific interventions rather than the "one-size-fits-all" approach that dominate the field of hypertension.

Compliance with Ethics Guidelines

Conflict of Interest Majd AlGhatrif and Edward G. Lakatta declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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