# Aortic Stiffness: Review of Life Course, Epidemiology, Risk Factors, and Relevant Biomarkers

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Scholarly Report Title: Aortic Stiffness: Review of Life Course, Epidemiology, Risk Factors, and Relevant Biomarkers

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Aortic Stiffness: Review of Life Course, Epidemiology, Risk Factors, and Relevant Biomarkers

Introduction

Stiffening of the aorta, as measured by an increase pulse wave velocity (PWV) has been implicated as a predictor of worsened cardiovascular outcomes and mortality in both general community and high-risk conditions such as diabetes mellitus (DM), chronic kidney disease (CKD), hypertension (HTN), post-myocardial infarction (MI) and chronic inflammatory disease. In fact, quantification of aortic stiffness by measuring the carotid-femoral PWV (cfPWV) was proposed as an accepted ‘gold-standard’ to risk-stratify patients in the management of hypertension. It has been demonstrated to be a valuable independent predictor of cardiovascular risk in addition to traditional vascular risk factors. Further, there is evidence that it might reveal the presence of composite end-organ damage and has been shown to have superior prognostic value to office in ambulatory systolic blood pressure (SBP) in hemodialysis patients.

The arterial tree has varying mechanical properties along its length, primarily determined by different contributions of collagen and elastin to its structure, in addition to varying degrees of modulation by smooth muscle tone. Pulse waves generated secondary to pulsatile hemodynamics of the cardiac cycle travel down the large conduit arteries to the mid-sized arteries where they incur increased resistance due to branch points and increased arterial tone. The incident waves are then reflected back toward the central arteries from the periphery. The stiffness of the central conduit arteries determines the velocity with which the reflected waves return, with increased aortic stiffness resulting in more rapid propagation of reflected waves, determining the measured PWV.

The cfPWV is obtained via transcutaneous measurement of the PWV at the common carotid artery and at the femoral artery. The distance between the two surface sites and the time delay between the waveforms is used to determine the velocity component. Preferred standardized methods and conditions for this measurement have been described elsewhere. It is important to note that distending pressure also contributes to cfPWV, requiring a correction for mean arterial pressure (MAP), prior to interpreting cfPWV as a surrogate for stiffness. Brachial-femoral PWV (baPWV) method also exist, but because of PWV amplification in more peripheral arteries it is considered a less reliable measure of central artery stiffness, though there are many studies that have used this method. Another challenge of utilizing cfPWV has been the fact that the surface distance between carotid and femoral sites of measurement do not always correlate with arterial path-length, particularly in conditions such as obesity where it might be an overestimate and advanced age where vascular ectasia might cause an underestimate. Weber et al. proposed a scaling factor of 0.8 through a study that correlated invasive and surface measurements, which has been used in several large-scale studies. Magnetic resonance imaging (MRI) based techniques also offer promise due to their ability to
directly and accurately visualize path-length and ability to quantify stiffness in more proximal aortic segments, but thus far have not been validated for clinical use.\textsuperscript{36}

Pathologically increased arterial stiffness allows waves reflected from the periphery to return in phase with cardiac systole, augmenting central systolic pressure and increasing hemodynamic load on the left ventricle. The influence of aortic stiffness on central hemodynamics cannot be accurately reflected by peripheral blood pressure alone, likely explaining the ability of cfPWV to serve as an independent predictor of cardiovascular outcomes. Further, the processes implicated in arterial stiffness, which includes activation of oxidative stress pathways and inflammation may be reflective of underlying vascular risk.\textsuperscript{36}

Life-course

There is a well-characterized pattern of systolic hypertension and declining diastolic BP with increasing age. The physiology of this process has been attributed to stiffening of central arteries, resulting in a reduced arterial reservoir effect, augmenting pressure during systole and diminishing it during diastole.\textsuperscript{19} Increased central systolic pressures result in increased stress on left ventricular function and may play a role in deleterious processes such as left ventricular hypertrophy. Decreased diastolic pressures compound cardiovascular dysfunction by decreasing cardiac perfusion.\textsuperscript{52}

There are numerous mechanisms proposed that may contribute to age related arteriolosclerosis. Intrinsic age-related remodeling of arteries has been demonstrated with increasing intimal media (IM) thickness with age, in a manner that is more closely correlated with differences in age than with differences in atherosclerotic disease burden.\textsuperscript{51} Changes in the mechanical properties of the vascular media are also observed, with increased breaks in elastin and maladaptive remodeling with increased deposition of collagen. Age related arteriolosclerosis that is independent of atherosclerosis related damage is supported by the strong independent association between age and cfPWV that persists in the absence of atherosclerotic changes. It is also noted that though atherosclerotic changes are not necessary to for age-related stiffening, atherosclerosis, calcification and diabetes may also contribute to worsening stiffness. The cumulative exposure to vascular risk factors also serves as a potential explanation for increases in arterial stiffness with age.\textsuperscript{23}

Epidemiology

Despite having known prognostic implications distinct from traditional cardiovascular risk factors, the clinical use of cfPWV has been challenging due to limited knowledge of population specific reference ranges. The 2007 ESC/ESH guidelines proposed a cut-off value of 12 m/s based on clinical outcome data available at the time.\textsuperscript{44} However, cfPWV is significantly affected by factors such as age and blood pressure.\textsuperscript{52} Attempting to apply a singular cut-off value raises the
A European study utilizing the ‘Reference Values for Arterial Stiffness Collaboration Database’ was one of the first large-scale efforts to establish reference ranges for cfPWV in a healthy population. The database was populated by thirteen centers across 8 European countries. The investigators excluded subjects with overt CVD and subjects with HTN, dyslipidemia, or both, requiring treatment. The study population was further sub-grouped into a normal population that had optimal blood pressure and did not have risk factors defined as dyslipidemia, smoking or both. The ranges for the reference population were based on the normal group and those with risk factors including high normal BP, high BP, dyslipidemia and smoking or both. Different algorithms were used to measure cfPWV across different centers, and it has been previously determined that this can introduce a 5-15% difference in measured PWV. The investigators noted that even after full adjustment between path-length and algorithm a difference remained (0 +/- 0.59 m/s, range -0.9 to 0.8 m/s). Based on existing data, surface level path-length measurements were likely to overestimate the true distance from carotid-femoral points of wave reflection, therefore cfPWV was multiplied by a correction factor of 0.8 to improve correlation with true path-length. The cfPWV ranges for the reference were elevated compared to the normal subgroup, with differences primarily driven by age and BP level, with negligible contribution by factors such as gender, smoking, and dyslipidemia.

An Angolan study attempted a similar effort in establishing reference and normal ranges in a cohort of employees of a public university in Luanda, Angola. A sample of 301 employees who were confirmed to have a BP <140/80 were selected as a the reference population. A subset of 131 subjects with optimal BP (<130/85) and without classical CV risk factors such as DM, smoking, obesity, dyslipidemia, and history of alcohol abuse was defined as the healthy group (HG). Similar to the aforementioned European study, the Angolan investigators noted that the cfPWVs were elevated in the reference group compared to the reference population. They also noted consistent values for cfPWV in the HG <30 and 30-39 age groups with those proposed by the European investigators, positing that ethnicity related differences might only be apparent in older patients. However, they noted that a direct comparison between older subjects in their study and the European study could not be directly compared, given an elevated burden of risk factors among the African population, thus raising the issue of uncertainty regarding substrate level differences among ethnicities versus risk factor burden or susceptibility to risk factors as the mediator of differential progression of arterial stiffness. The investigators also noted that male gender was associated with increased PWV only among the group with CVD risk factors, but not in the HG, suggesting gender-modulation of stiffness in the presence of risk factors. However, it was one of the few studies that found an association with gender among the studies seeking to
establish reference ranges. A similar trial was conducted in Argentina and its focus was a cohort in the city of Tendil. The investigators of this trial attempted to create reference values based on a cohort of 760 subjects, with exclusion criteria including dyslipidemia, DM, CVD, CKD, HTN, smoking, obesity, or history of hypertension in first degree relative. The investigators decision to exclude relatives of hypertensives stemmed from an effort to minimize the effect of heritable variables that may be associated with polymorphisms affecting cfPWV. As in previous studies, they noted no difference in PWV with based on gender and noted that it was primarily driven by age. They also noted that cfPWV dispersion increased with age >50 as observed in other studies, suggesting that differences represent a unique conglomerate information point that may not be reflected by the effects of age or traditional risk factors alone.

Investigators in Uruguay who attempted to establish reference ranges studied a population drawn from the CUiiDARTE Project, a population-based national study. This study also used conservative exclusion criteria including those with CVD, DM, smoking, anti-hypertensive or lipid lowering medications. In addition, they excluded those with plaque in the carotid arteries, identified with Doppler ultrasound. This group found no association with gender and found that increased cfPWV was associated with increasing age and hypertension. This group utilized the “accepted method” of defining PWV, but also employed other algorithms and noted that different algorithms produced a difference in mean PWV of >20%, highlighting the need for adherence to a standard protocol to allow for population level comparisons.

The most recent effort was from the ELSA-Brasil Study, a multicenter cohort of adult Brazilian public servants. The study subjects were selected based on strict exclusion criteria including no DM, optimal and normal BP (SBP <130 or DBP <85) without BP lowering medications, BMI 18.5-25, no history of smoking and no CVD. The analysis demonstrated that cfPWV was strongly correlated to age and BP. However, the authors also noted an independent association with gender and therefore present sex-specific ranges. The investigators then compared the age-related increase in cfPWV between the healthy group and the entire ELSA-Brasil population (n=14,733). The presence of risk factors doubled the age related increase in cfPWV, however the cfPWV ranges remained similar until approximately age 40. This highlights the notion that risk factors compound expected age-related increases in cfPWV, and also suggests the possibility of early risk reduction to prevent late end-organ damage.

Race
There is mixed data regarding the issue of racial differences in markers of arterial function. However, it is important to note that blacks suffer a disproportionately increased risk of CVD, HTN and microvascular dysfunction compared to whites, highlighting that racial differences do exist in terms of morbidity and mortality in vascular health. There is data to suggest that these differences may be driven by a difference in risk factor burden or sensitivity to incident risk factors. There is also evidence that point to intrinsic differences in mechanical properties of blood vessels and differential remodeling in response to oxidative and mechanical stressors.

A group of investigators used the ELSA-Brasil database to interrogate if (1) differences in arterial stiffness exist between different racial groups and (2) if those differences persisted after adjusting for vascular risk factors. The investigators used self-declared race including blacks, browns, and whites for the analysis. They noted that blacks had a higher burden of HTN, DM and obesity compared to the other groups and had higher unadjusted cfPWVs compared to browns and whites who were similar. However, after adjusting for MAP, age, waist circumference (WC), HR, and fasting glucose, the inter-group differences were abrogated. A sub-group analysis of black and brown women in the highest cfPWV quartile revealed that arterial stiffness was elevated in these two groups even after adjusting for covariates. The results of this study indicate that ~40% of inter-group variance could be explained by age and MAP, suggesting that modulation of MAP may be the most important way to abrogate racial differences in progression of arterial stiffness. Though there may be a race-gender interaction in women, the strength of that relationship was much weaker than the effects of MAP and age. The HELISUR investigators highlighted the importance of addressing hypertension in non-white populations. In their study of 1,157 subjects of predominantly Asian and African subjects in Suriname, they noted that while 71% had HTN or pre-HTN, only 20% demonstrated adequately controlled BP.

Other investigators have noted that the difference in cfPWV among different ethnicities seems to be driven by either differential exposure to risk factors or differential sensitivity to them. A group in Amsterdam studied 4 major ethnic groups including Dutch, South-Asian Surinamese, African Surinamese and Ghanaian utilizing the HELIUS study database. The investigators noted choosing two ethnic groups of West African ancestry given that they would be expected to have similar migration patterns and genetic footprints, which would suggest that concordant differences in cfPWV may be driven by intrinsic differences in structure or remodeling. The investigators noted that elevated cfPWV relative to whites was only apparent in South Asian Surinamese, but only above age 40 and for Ghanaian women below age 50. Given that the differences were only evident with advancing age, and in one subset of one West African group, the investigators suggested that this more likely represents a difference in risk factor burden and sensitivity. For instance, they noted that South Asians had worse waist-to-hip ratios (WHR) and that Ghanaian women had worse HTN profiles.
The notion that certain ethnicities are more susceptible to vascular risk factor induced damage is reported elsewhere in the literature. Birru et al reported that cfPWV progression was affected by risk factors such as DBP, glucose and LDL-C in African American women, while it was not in Caucasian women. There is some evidence that points to hyper-responsive remodeling as the cause of these differences. The Keloid Hypothesis proposes that enhanced sensitivity of cfPWV to hypertension in blacks may stem from abnormal VSMC response to inflammatory cytokine mediators. Keloid fibroblasts in culture demonstrate an abnormally increased sensitivity to mediators such as TGF-B and Platelet Derived Growth Factor (PDGF), resulting in increased production of extracellular matrix components.

The Multi-Ethnic Study of Atherosclerosis (MESA) investigators studied stiffness parameters including wall thickness (WT) and aortic distensibility (AD) via MRI. The study noted that while WT did significantly differ between African Americans and whites, decreased AD was independently associated with African American race. Investigators noted similar results while studying a cohort from the Dallas Health Study (DHS). They studied proximal aortic arch stiffness via MRI, and found that African Americans and Hispanics had greater aortic arch PWV (aPWV). The characteristic impedance (Zc), which is proportional to wall stiffness and inversely proportional to diameter, was also elevated in African Americans and Hispanics compared to whites. Further, they noted that Hispanics and African Americans had smaller aortic areas compared to whites. The relationship disappeared when correcting for height in Hispanics, but remained in African Americans, suggesting a possible impairment in compensatory remodeling to increased cardiac output (CO) or HTN.

There is also data that demonstrates that differences in markers of arterial stiffness exist among young, healthy subjects of different races, indicating intrinsic differences in the properties of vessels or unmeasured risk factors. Observations from the Bogalusa Heart Study demonstrated that a divergence in measures of arterial compliance could be seen in otherwise asymptomatic young adults, with African American young adults having lower arterial compliance compared to Caucasian American counterparts. A South African study demonstrated that differences in vascular stiffness might be seen as early as in children of 6-8 years. They noted that while black boys tended to have elevated MAP, intimal media thickness (IMT), and cfPWV compared to white boys. A study in Syracuse produced slightly differing results. The investigators noted that no there was an elevation of cfPWV in black boys relative to white boys. However, they did not note an association between black race and increased IMT. IMT is considered a better predictor of the presence of atherosclerosis than arteriolosclerosis. Therefore, it implicates intrinsic differences in vascular composition or early remodeling rather than accelerated atherosclerosis as would be expected in young, healthy subjects.

Some investigators posited, that the differences in young healthy populations and the presumed differences in sensitivity to risk factors might be attributed to other unmeasured risk factors. For instance, it has been demonstrated that some ethnic
groups living in the northern hemisphere likely suffer a greater burden of Vitamin D deficiency relative to white counterparts. Vitamin D has been proposed to improve vascular health by suppressing oxidative pathways and the sensitivity to RAAS mediated remodeling. However, there are inconsistent results regarding the impact of Vitamin D supplementation on measures of arterial stiffness such as cfPWV. One double-blind randomized controlled trial (RCT) demonstrated a dose-response improvement in PWV during a 12-week follow-up period. However, the paucity of large-scale studies suggests the need for further research to determine the clinical utility of improving Vitamin D to improve vascular health.

Generalized endothelial dysfunction has also been posited as a mediator of progressive arterial stiffness in blacks compared to whites. Studies have demonstrated that blacks tend to have impaired response to NO mediated vasodilation. Morris et al. demonstrated that the reactive hyperemia index (RHI), a measure of NO mediated microcirculatory function and PWV was concordantly elevated in blacks compared to whites. A subgroup analysis of the cohort revealed that even among low-risk individuals with no traditional risk factors for cardiovascular disease, the RHI and PWV was elevated in blacks compared to whites, suggesting that impaired vascular function precedes incident disease.

**Risk Factors**

**Hypertension:**

Hypertension demonstrates a very strong association with measures of arterial stiffness, compared to other cardiometabolic risk factors studied. A major shift has occurred with regards to the understanding of directionality between the nature of the influence of hypertension on arterial stiffening and vice versa. The initial paradigm posited that arterial stress induced by elevated pressure and pulsatility mediated breaks in elastin, along with resulting in maladaptive remodeling by inducing inflammation. However, clinical and experimental studies now demonstrate that the relationship between hypertension and arterial stiffness is bidirectional.

It has been demonstrated that ongoing hypertension accelerates progression of arterial stiffness. Investigators of the CRAVE study demonstrated that the progression of arterial stiffness measured by PWV is modulated by pre-existing cardiovascular risk factors including hypertension and dyslipidemia, even when controlled without changes in pharmacologic management over a follow-up time of two years. Further, when comparing the rate of progression in subjects with hypertension alone (0.193 m/s/year) to that of those with both hypertension and dyslipidemia (0.398 m/s/year), a four-fold higher rate of progression was noted suggesting a synergistic effect. In addition, blood pressure variability has also been linked to increased measures of vascular stiffness. Shear stress can result in increased generation of transcription factors including platelet-derived growth factor (PDGF) in vascular endothelium, which can stimulate myoproliferation in the
vessel wall, providing potential mechanistic explanation for the observed effects of high BP and BP variability.\textsuperscript{71}

The development of increased arterial stiffness preceding the development of over hypertension has been described in mice and humans. Several longitudinal studies have demonstrated that increases in PWV precede the development of clinical hypertension. Investigators utilizing participants of the Framingham Heart Study demonstrated that initial PWV values were predictive of incident hypertension.\textsuperscript{28} Investigators from the Baltimore Longitudinal Study of Aging (BLSA) also found that increased PWV was predictive of incident hypertension and that increased PWV predicted longitudinal increase in BP.\textsuperscript{51} Weisbrod et al. demonstrated that diet-induced obese mouse developed increases in PWV within two months of diet initiation. Molecular studies indicated an elevation of TNF-alpha, increased markers of oxidative stress and impaired NO production in approximately the same timeframe. These findings preceded the development of hypertension, suggesting that endothelial dysfunction and inflammation induced impairment in vasoreactivity may be causal.\textsuperscript{73}

RAAS

The role of RAAS in the progression of arterial stiffness is supported by observational studies, clinical studies relating to modulation with therapeutics, biochemical studies demonstrating involvement in vascular remodeling, and mapping of related gene loci.

Studies have demonstrated an association of increased aldosterone to renin ratio (ARR) with increased PWV.\textsuperscript{54} RAAS inhibition through renin and aldosterone modulation has been shown to produce direct decreases in measures of arterial stiffness compared to beta-blockade. London et al. demonstrated that central systolic blood pressure (SBP) was decreased to a greater extent in with perindopril/indapamide treatment compared to treatment with atenolol, without a significant difference in peripheral SBP, implying a distinct role of RAAS modulation in central hemodynamics.\textsuperscript{41}

Selective mineralocorticoid blockade with eplerenone has been shown to decrease concentrations of inflammatory markers including MCP-1, basic fibroblast growth factor, interleukin-1 and interleukin-10. The ability to result in arterial structural changes by reducing the collagen/elastin ratio in the media has also been observed.\textsuperscript{65} Transgenic mice overexpressing human angiotensinogen and renin genes were found to have upregulated nuclear factor kB (NFkB) mediated through angiotensinogen II and endothelin mediated signaling, suggesting increased vascular oxidative stress. The same models demonstrated premature death secondary to cardiac and renal failure, with microvascular abnormalities including fibrinoid vasculopathy. Interestingly, suppressing oxidative stress by inhibiting NFkB was protective against deleterious vascular changes while blood pressure modulation by non-RAAS inhibition was ineffective, suggesting that activation of
oxidative pathways may be the more consequential modulator of vascular structure compared to mechanical stress alone.\textsuperscript{53} Further, an in vivo study has demonstrated that Epithelial Sodium Channel (ENaC), modulated by mineralocorticoids, plays a role in regulation of nitric oxide production and endothelial function. Thereby, posing another mechanism by which mineralocorticoids may affect arterial function.\textsuperscript{67}

Therapeutically, modulation of RAAS has been shown to produce greater reduction in cfPWV compared to beta-blockade, despite achieving similar reductions in peripheral pressures. Kourmaras et al demonstrated that when comparing atenolol, nevibiol, aliskerin and quinapril, the RAAS modulating agents demonstrated sustained reductions of PWV at both two and ten weeks, while the other agents did not, possibly implicating arterial remodeling rather than modulation of hemodynamics alone.\textsuperscript{31} Further, decreased salt intake has been shown to decrease arterial stiffness independent of blood pressure reduction and may mediated through RAAS modulation.\textsuperscript{11}

The importance of RAAS is the pathogenesis is further highlighted by a study of hypertensive patients that demonstrated a positive association between cfPWV and a polymorphism in the angiotensin II type 1 receptor (AT1R). Interestingly, the investigators noted the possibility of dose responsiveness given heterozygotes at AT1R had an aortic stiffness intermediate to homozygotes at either end of the spectrum. Other components of RAAS such as angiotensin converting enzyme alleles and aldosterone synthase alleles have been variably implicated, as there have been studies showing and refuting associations.\textsuperscript{5,34,57} Interestingly, aortic stiffness and blood pressure are known to be highly heritable, and the contribution of RAAS polymorphisms may act as one potential contributor.\textsuperscript{35}

**Metabolic Syndrome**

There is evidence to suggest that both Diabetes Mellitus (DM) and the Metabolic Syndrome (MetS) have been associated with increased vascular stiffness and that increased PWV is associated with worse CVD mortality in DM.\textsuperscript{45} The close relationship between MetS and arterial stiffness is demonstrated by the fact that a High-Fat/High-Fructose (HFHF) diet, used to simulate MetS in mice produces increased arterial stiffness.\textsuperscript{55}

Investigators from the Bogalusa Heart Study studied asymptomatic, healthy black and white subjects between the ages of 24-44. This cross-sectional study demonstrated that the slope of expected age-related increase in baPWV was modulated by number of metabolic syndrome components.\textsuperscript{39} Investigators from the MARK study similarly noted that MetS components were associated with elevated baPWV and found a sex association that indicated males with MetS suffer greater arterial stiffness.\textsuperscript{25} An interesting dose dependent relationship between level of glucose dysregulation and elevation of PWV has also been described. A study by
Petri et al studied 500 subjects characterized as having normal glucose metabolism, impaired glucose tolerance, and overt DM and noted a progressive increase in PWV between groups with worse glucose regulation. The relationship between pre-diabetic glucose dyregulation and arterial stiffness is not supported by all studies. For instance, the investigators from the MARK study found a positive association between fasting plasma glucose (FPG), postprandial glucose (PG), and glycosylated hemoglobin (HbA1c), however these associations were only maintained in those with overt DM after correction.

There are also prospective studies that support the cross-sectional associations between MetS and arterial stiffness, lending support to causal relationship. A prospective study by Safar et al followed 476 subjects for 6 years demonstrated that there was a stepwise increase in PWV in groups with 3 or more MetS risk factors compared to 2 or less. A prospective study of 2080 male subjects in Japan similarly established that PWV was elevated in individuals with MetS compared to controls. The study also noted that there was a reversal of PWV in individuals with regression of MetS compared those with persistent MetS over a 3-year follow-up.

The pathogenesis of arterial stiffness in MetS and DM is likely to be mediated by the pro-inflammatory milieu generated by metabolic dysregulation and direct damage to the vascular wall. Di Pino et al. demonstrated that high intake of advanced end glycation products (AGEs) was associated with higher PWVs among diabetics. A trial of ALT-711, a nonenzymatic breaker of AGEs, decreased PWV in the elderly. Therefore, modulation of AGEs remains an interesting target to halt disease progression.

**Inflammation**

The presence of chronic inflammatory and infectious conditions such as systemic lupus erythematosus (SLE) (Sacre), inflammatory joint disease (IJD), inflammatory bowel disease (IBD), psoriasis, gallstone disease and Human Immunodeficiency Virus have been linked with elevated risk of CVD. Cross-sectional studies have also demonstrated elevated PWV in cohorts of patients with IJD, SLE and IBD. The accelerated vascular disease in these cohorts that are lower risk in terms of traditional vascular risk factors, suggests that chronic inflammation may contribute to progressive vascular stiffness and dysfunction.

A recent prospective study also demonstrated a longitudinal association between chronic elevation in inflammatory markers and progression of PWV and BP. The study followed 3274 middle-aged Japanese men without hypertension for a follow-up period of 9 years. The investigators demonstrated that sustained elevation in serum CRP was correlated with a longitudinal increase of baPWV. The increased baPWV was in turn associated with higher blood pressures during follow-up.

Similar to patients with chronic inflammatory disorders, patients with CKD also suffer from a disproportionately elevated risk for CVD mortality and morbidity not
explained by traditional risk factors alone. A study of patients with CKD investigated
the relationship between inflammatory markers including IL-6, IL-1β, and TNF and
aortic stiffness, and found an association between IL-6 levels and PWV.12 Another
study demonstrated that Neutrophil-to-Lymphocyte ratio (NLR) was correlated
with elevated baPWV in patients on peritoneal dialysis (PD).7 There are no large-
scale prospective studies to imply causality between elevated arterial stiffness and
inflammatory markers in this population, but these associations suggest the need
for investigation of the contribution of inflammation in accelerated vascular
stiffness in patients with CKD.

There is a paucity of large studies evaluating the effects of anti-inflammatory drugs
on modulating aortic stiffness. A meta-analysis of studies on the effects of anti-
tumor necrosis factor a (TNF-a) agents on measures of arterial stiffness in patients
with RA demonstrated significant improvements in cfPWV after treatment.72 There
may also be a role for statins as demonstrated by a recent study that demonstrated
improvement in baPWV correlated with clinically significant improvements in BP in
patients with IJD following 18 months of treatment with rosvustatin. However, no
correlation was found between LDL-c or inflammatory markers (ESR/CRP) and
improvement in stiffness, so the mechanism by which stiffness is affected in this
scenario remains unclear.27

Uric Acid

Uric acid has been implicated in oxidative stress and endothelial dysfunction. Cross-
sectional studies to date have had disparate findings with concerning the
association between serum uric acid (SUA) concentration and PWV. Investigators
from the Framingham Heart Study (FHS) demonstrated an association between
higher uric acid and cfPWV in a community-based cohort.46 Investigators using the
ELSA-Brasil database noted that the association between SUA and cfPWV only
persisted in men.2 Investigators from BLSA demonstrated that women in the highest
tertile serum uric acid (>4.9) PWV was associated with age at entry, while for men
in the highest tertile serum uric acid (>6.2) was associated with accelerated PWV
increase over time. Given that men have elevated serum uric acid compared to
women at all ages, and the association is only observed in the highest tertile SUA for
men, the authors posit a threshold effect of SUA on vascular stiffness that is more
commonly achieved in men.8 In contrast, investigators studying a cohort from the
Brisighella Heart Study noted that while HTN and IMT were associated with
increasing SUA, cfPWV was not.10 Interestingly, a randomized controlled trial that
tested endothelial function in response to xanthine oxidase inhibition found that
high-dose allopurinol abolished oxidative stress and improved endothelial function,
however, it did not affect circulating levels of uric acid, raising the possibility that
circulating uric acid is a surrogate for processes that result in endothelial
dysfunction.22

Biomarkers
Sirtuin-1/Klotho

Klotho, known as the “anti-aging” gene, encodes a transmembrane primarily expressed in the renal distal tubules and choroid plexus, along with a cleavage product that circulates systemically and is known to decline with age. Klotho +/- haplodeficient mice models with reduced levels of circulating Klotho, demonstrate accelerated aging including progressive arterial stiffness, hypertension and atherosclerosis.

SIRT1 is a gene encoding a NAD+-deacetylase, with anti-inflammatory, anti-oxidant effects and is expressed in endothelial and vascular smooth muscle cells. It is thought to promote vascular health through downstream modulation of eNOS and AMP-Activated Protein Kinase, which suppress oxidative stress pathways. SIRT1 expression has been associated with decreased expression of inflammatory mediators, NFkB and vascular cell adhesion molecule 1 (VCAM1). Klotho +/- mice demonstrate reduced expression of SIRT1 in endothelial and vascular smooth muscle cells. Histologically endothelial cells and VSMCs of these mice demonstrate a high burden of elastin breaks and increased collagen deposition. Overexpression of SIRT1 using a small molecule activator, SRT720, reversed arterial stiffness and oxidative stress down to control levels in Klotho +/- mice without altering circulating Klotho levels, implying that SIRT1 expression is a downstream target for modulation. SIRT1 expression is also diminished in mice fed HFHS Diet, which demonstrate increased arterial stiffness. In these mice, overexpression of SIRT1 using SRT720 resulted in improved arterial stiffness without affecting weight or metabolic profile, suggesting that the metabolic syndrome may also regulate the expression of SIRT1 and amenable to bypass with downstream stimulation. Improvements in PWV after an overnight fast in HFD mice was associated with increased SIRT1 expression.

In addition to suppression of anti-oxidant pathways, Klotho deficiency has also been associated with upregulated oxidative stress. Elevated levels of matrix metalloproteinases (MMP-2, MMP-10) and transforming growth factor β are expressed in the aortas of Klotho deficiency. Zhou et al. demonstrated that CYP11B2, a rate-limiting enzyme in aldosterone synthesis, is upregulated in Klotho deficiency. Treatment with eplerenone reversed both increased stiffness and diminished oxidative inflammation, suggesting that depressed Klotho may mediate increased arterial stiffness through aldosterone mediated remodeling.

In patients with CKD, Klotho levels independently predicted arterial stiffness measures by brachial-ankle pulse wave velocity (baPWV), in addition to being associated with decreased intact parathyroid hormone (PTH) and elevated 1,25 Vitamin D. Klotho haplodeficiency in mice produces a phenotype that is similar to CKD with dysregulated calcium homeostasis and hyperphosphatemia. Diminished levels may dysregulate calcium homestasis. In fact Klotho knockout mice, develop ectopic calcification and die within 8 weeks. In vitro studies of human artery
vascular smooth muscle (HA-VSMC) indicate that local deficiency of Klotho allows upregulation of Runx2, facilitating osteoblastic differentiation of VSMCs resulting in calcification and loss of contractile function.\textsuperscript{33,40}

Klotho and its downstream target SIRT1 have enumerated a number of possible targets for therapeutic modulation that target pro-oxidant and pro-inflammatory pathways. Further, improved calcium and phosphate homeostasis may be of increased importance in CKD patients where impaired calcium homeostasis and a pro-inflammatory milieu may accelerate vascular dysfunction. Klotho mediated upregulation of aldosterone and the reversibility of deleterious vascular changes using eplerenone suggests the possibility of using existing drugs to target arterial stiffness for risk reduction.

Conclusion

Aortic stiffness is an accepted risk factor for CVD risk. Despite its demonstrated prognostic value, widespread clinical use has thus far been limited by variation in methodology and lack of age and blood pressure specific reference values applicable to all populations. The upsurge in studies aiming to establish reference ranges for risk stratification is promising as there are targetable pathways and therapies that have been identified that may be useful for risk factor modification. In addition, the use of MRI based techniques to more accurately characterize path-length and provide a more detailed segment by segment analysis of the aortic stiffness may provide more accurate and granular data into the pathogenesis of aortic stiffness and its downstream cardiovascular consequences.

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Supplementary Material

Table 1. Synopsis of “Normal” Ranges Established by Reference Studies

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<td>Healthy residents of the city of Tendil, Argentina</td>
<td>High BP, History of CVD, DM, Serum Cr &gt;1.5, Smokers, Triglycerides (TG) &gt; 150, Total Cholesterol (TC) &gt; 200, HTN in 1st degree relative, Body Mass Index (BMI) &gt; 30</td>
<td>Motorola MP 20150, Motorola Inc.</td>
<td>Direct Path Length x 0.8</td>
</tr>
<tr>
<td>Age Group</td>
<td>N</td>
<td>Mean PWV (m/s)</td>
<td>SD</td>
</tr>
<tr>
<td>10-19</td>
<td>156</td>
<td>5.04</td>
<td>0.72</td>
</tr>
<tr>
<td>20-29</td>
<td>110</td>
<td>5.86</td>
<td>0.92</td>
</tr>
<tr>
<td>30-39</td>
<td>109</td>
<td>6.32</td>
<td>0.82</td>
</tr>
<tr>
<td>40-49</td>
<td>108</td>
<td>6.85</td>
<td>0.91</td>
</tr>
<tr>
<td>50-59</td>
<td>164</td>
<td>8.15</td>
<td>1.17</td>
</tr>
<tr>
<td>60-69</td>
<td>103</td>
<td>8.47</td>
<td>1.09</td>
</tr>
<tr>
<td>&gt;70</td>
<td>30</td>
<td>9.01</td>
<td>2</td>
</tr>
</tbody>
</table>

Population (Magalhaes et al)

| Age Group | N | Mean PWV (m/s) | SD |
| <30 | 47 | 6.1 | 0.8 |
| 30-39 | 41 | 6.4 | 0.7 |
| 40-49 | 43 | 7.3 | 0.9 |
| ≥50 | 131 | 6.6 | 1 |

Population (Baldo et al.)

| Age Group | N | Mean PWV (m/s) | SD |
| <30 | 47 | 6.1 | 0.8 |
| 30-39 | 41 | 6.4 | 0.7 |
| 40-49 | 43 | 7.3 | 0.9 |
| ≥50 | 131 | 6.6 | 1 |
15,105 active and retired employees aged 35-74, Brazilian public servants from 6 different regions of Brazil. Exclusion criteria included fasting blood glucose ≥ 126, glycated hemoglobin > 6.5%, 2-hr post-load plasma glucose >200, anti-DM medication, systolic BP >130, diastolic BP >85, BP lowering drugs, BMI ≥ 25 kg/m^2, ≤ 18.5 kg/m^2. Subjects referred for cardiovascular evaluation in the CUiiDARTE Project, Uruguay. Exclusion criteria included known CVD, smoking, atherosclerotic plaque in carotid arteries with ultrasound, DM, CKD, antihypertensive medication, lipid-lowering medication.

<table>
<thead>
<tr>
<th>Age</th>
<th>N (Men)</th>
<th>Mean PWV (m/s)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-44</td>
<td>334</td>
<td>8.53</td>
<td>1.14</td>
</tr>
<tr>
<td>45-54</td>
<td>275</td>
<td>8.81</td>
<td>1.24</td>
</tr>
<tr>
<td>55-64</td>
<td>109</td>
<td>9.48</td>
<td>1.39</td>
</tr>
<tr>
<td>65-74</td>
<td>27</td>
<td>10.36</td>
<td>1.67</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>N (Women)</th>
<th>Mean PWV (m/s)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-44</td>
<td>567</td>
<td>8.25</td>
<td>0.99</td>
</tr>
<tr>
<td>45-54</td>
<td>539</td>
<td>7.82</td>
<td>1.17</td>
</tr>
<tr>
<td>55-64</td>
<td>255</td>
<td>8.27</td>
<td>1.31</td>
</tr>
</tbody>
</table>

Population (Farro et al.) Exclusion Device Path-Length Correction Factor

<table>
<thead>
<tr>
<th>Age Group</th>
<th>N</th>
<th>Mean PWV (m/s)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-19</td>
<td>61</td>
<td>6.1</td>
<td>0.9</td>
</tr>
<tr>
<td>20-29</td>
<td>103</td>
<td>7.2</td>
<td>1.3</td>
</tr>
<tr>
<td>30-39</td>
<td>60</td>
<td>8.2</td>
<td>1.2</td>
</tr>
<tr>
<td>40-49</td>
<td>71</td>
<td>8.9</td>
<td>1.6</td>
</tr>
<tr>
<td>50-59</td>
<td>66</td>
<td>9.4</td>
<td>1.8</td>
</tr>
<tr>
<td>60-69</td>
<td>68</td>
<td>12.5</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Population (Reference Values for Arterial Stiffness’ Collaboration) Exclusion Device Path-Length Correction Factor
### Reference Values for Arterial Stiffness Collaboration Database:
Population from 13 centers across 8 European Countries

<table>
<thead>
<tr>
<th>Age</th>
<th>N (Normal)</th>
<th>Mean PWV m/s</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>896</td>
<td>6.2</td>
<td>0.75</td>
</tr>
<tr>
<td>40-49</td>
<td>822</td>
<td>7.2</td>
<td>1.3</td>
</tr>
<tr>
<td>30-39</td>
<td>315</td>
<td>6.5</td>
<td>1.35</td>
</tr>
<tr>
<td>50-59</td>
<td>514</td>
<td>8.3</td>
<td>1.9</td>
</tr>
<tr>
<td>60-69</td>
<td>414</td>
<td>10.3</td>
<td>2.4</td>
</tr>
<tr>
<td>≥70</td>
<td>163</td>
<td>10.9</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Overt CVD, DM, HTN Treatment, Dyslipidemia Treatment, HTN and Dyslipidemia Treatment, High/High Normal BP, Dyslipidemia, Smoking, Smoking and Dyslipidemia

Varied across centers, most used systems include Complior and Syphgmacor

Direct Path Length x 0.8