Review

Arterial Stiffness: A Nexus between Cardiac and Renal Disease

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Abstract

Vascular disease is the leading cause of morbidity and mortality in the Western world, and vascular function is determined by structural and functional properties of the arterial vascular wall. Cardiorenal metabolic syndrome such as obesity, diabetes, hypertension, kidney disease, and aging are conditions that predispose to arterial stiffening, which is a pathological alteration of the vascular wall and ultimately results in target organ damage in heart and kidney. In this review, we provide new insights on the interactions between arterial stiffness, vascular resistance and pulse wave velocity as well as final end-organ damage in heart and kidney. Better understanding of the mechanisms of arterial functional and hemodynamic alteration may help in developing more refined therapeutic strategies aimed to reduce cardiovascular and chronic kidney diseases.   © 2014 S. Karger AG, Basel

Introduction

Arterial stiffness (AS) is the consequence of structural and functional changes of the vascular wall that occur in response to cardiorenal metabolic syndrome (CRS), injury, or aging [1]. Although AS can be regarded as a mechanism that naturally occurs with aging, AS is associated with significant hemodynamic changes, target organ damage, and increased cardiovascular morbidity and mortality (fig. 1) [2]. The Framingham Heart Study of 2,232 participants confirmed AS an independent predictor of cardiovascular morbidity and mortality in the general population, hypertensive patients, the elderly, and patients with end-

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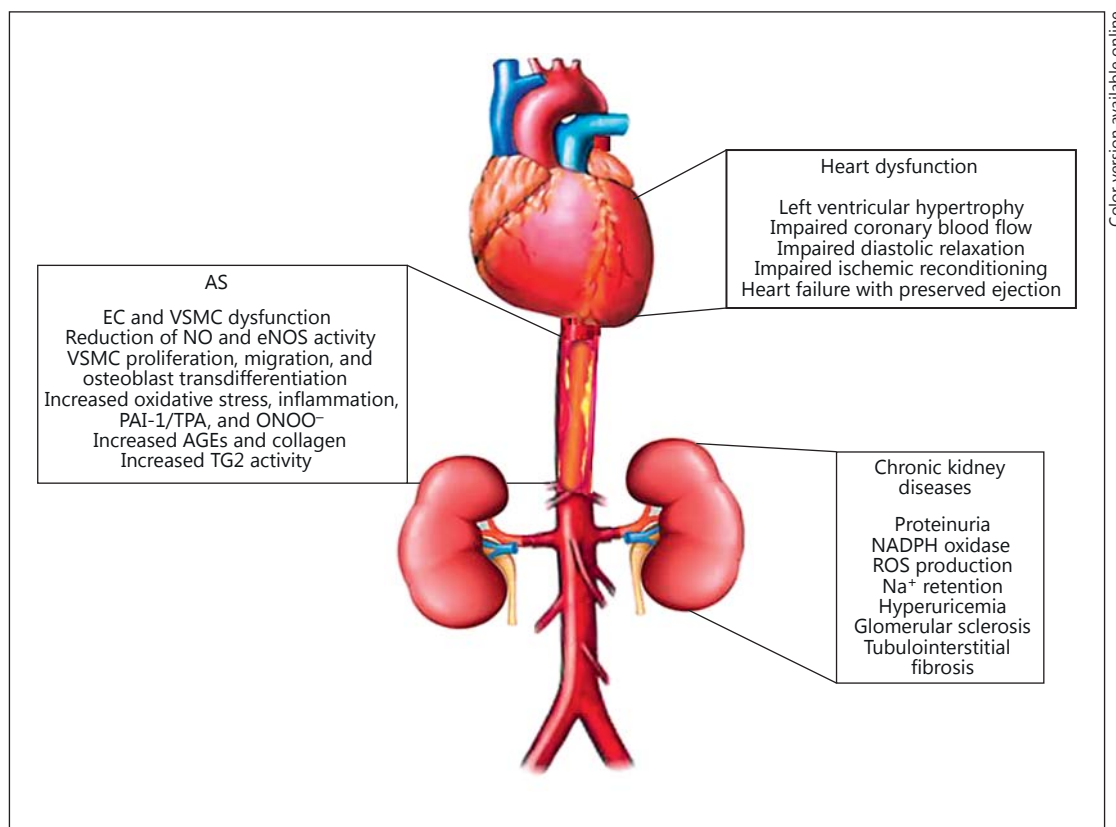
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Fig. 1. Proposed interactions among AS, vascular resistance, and organ damage in heart and kidney. AS increases PWV resulting in LV remodeling and kidney dysfunction, and thereby causes LVDD and development of CAD. Conversely, kidney dysfunction further aggravates arterial injury. PAI = Plasminogen activator inhibitor; TPA = tissue plasminogen activator; ONOO⁻ = peroxynitrite.

stage renal disease [3]. Measurements of AS include central pulse pressure/stroke volume index, pulse wave velocity (PWV), total arterial compliance, pulse pressure amplification, and augmentation index [4]. Recently, the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines for the management of arterial hypertension suggested the measurement of aortic PWV, which is considered the gold standard method for assessing AS, as a tool for assessment of subclinical target organ damage [5]. Typical values of PWV in the aorta range from approximately 5 to >15 m/s [4]. A fixed threshold value (12 m/s) was proposed as AS in the 2007 ESH/ESC hypertension guidelines based on published epidemiological studies [6].

Recently, studies have shown that morbidity and mortality in cardiovascular diseases (CVD) are greatly enhanced in patients with chronic kidney disease (CKD), compared to the nonrenal disease population [7]. One key element related to AS, increased proteinuria, is linked to a decreased glomerular filtration rate (GFR) and is predictive of kidney disease progression [8]. Indeed, renal dysfunction has been shown to increase AS via several mechanisms, including vascular calcification, chronic volume overload, inflammation, endothelial dysfunction, oxidative stress, and overproduction of uric acid. Conversely, AS attenuates arterial compliance to dampen pulsations from the left ventricular (LV) ejection, resulting in microvascular damage, especially in the kidney [9]. Thus, AS and renal dysfunction might have a cause-effect relationship, and complicated molecular biology mechanisms modulate

their bidirectional causal relationship. Undoubtedly, the mechanisms underlying AS in CVD and CKD are complex, and an understanding is paramount to enable the development of novel therapeutic strategies to prevent or reverse this pathophysiology and therefore reduce the risk of developing CVD and CKD. The objectives of this review are to provide a basic overview of AS and its role in the development of CVD and CKD.

AS and Ventricular-Arterial Coupling

The physiology of AS is now better understood by the measurement of PWV. When heart contraction generates a PWV that travels through the circulation, a pulse wave is generated and propagated forward to the peripheral arterial system. The blood pressure wave is then reflected back to the heart from branching points of peripheral arteries. The final pressure waveform at the aortic root is the summation of the forward traveling wave and the reflected wave [10]. In healthy individuals with normal arteries, the reflected wave merges with the forward traveling wave in diastole and augments coronary blood flow. In patients with AS due to aging or vascular diseases, the reflected wave returns faster and merges with the forward wave in systole resulting in augmentation of systolic blood pressure and pulse pressure, and therefore hypertension [11]. This causes an increase in LV afterload and decreased coronary perfusion. Thus, the pathophysiological and clinical implications of AS should be considered together with the cardiac function, since the interaction between the heart and the arterial system is widely known as the 'ventricular-arterial coupling', and can be a key determinant of CVD performance [12].

It has been observed that age-related AS, which can seriously affect ventricular-arterial coupling, is accompanied by changes in the LV stiffness and diastolic compliance. The heart of the elderly appears to develop an increase in both diastolic and systolic LV stiffness with or without hypertrophy. As a consequence, the systemic circulatory compliance is reduced, generating larger changes in pressure for any given change in ejected volume and resulting in a greater blood pressure liability [13]. Another effect induced by ventricular-arterial stiffening is decreased coronary flow and regional coronary ischemia because of a decline in the ventricular systolic performance [14]. Furthermore, this combined ventricular-arterial stiffening, referred to as 'coupling disease', appears to be common in patients with heart failure (HF) and preserved ejection fraction [13]. Meanwhile, the arterial system in patients with CKD undergoes structural remodeling similar to changes due to aging and is characterized by diffuse dilation, hypertrophy, and stiffening of the aorta and major arteries, and consequently increased LV systolic stress and LV hypertrophy (LVH) [15]. Therefore, an increased systolic ventricular AS, together with left ventricular diastolic dysfunction (LVDD) and cardiac volume overload, is one of the pathophysiological mechanisms in HF with normal ejection fraction.

Cellular and Molecular Mechanisms of AS

AS is highly associated with CVD mortality, particular in patients with diabetes and CKD [7]. Risk factors include fibrosis, hyperplasia of the arterial intima and media, changes in vascular collagen and elastin, endothelial dysfunction, and vascular smooth muscle cell (VSMC) calcification and are involved in the development of AS.

Endothelial and VSMC Dysfunction in AS

The endothelium is a critical component to vascular homeostasis, actively responding to biochemical and physical stimuli through the release of a diverse set of vasoactive substances

[16]. The term 'endothelial dysfunction' refers to a maladapted endothelial phenotype characterized by reduced nitric oxide (NO) bioavailability, increased oxidative stress, elevated expression of proinflammatory and prothrombotic factors, and reduced endothelial derived vasodilation [17]. Insulin resistance, type 2 diabetes, and obesity are conditions that predispose to endothelial dysfunction. For example, insulin stimulates production of the vasodilator NO via activation of insulin receptor substrate (IRS)-1/phosphatidylinositide 3-kinases (PI3K) signaling in normal endothelial cells (ECs). However, endothelial insulin resistance is typically accompanied by reduced PI3K-NO signaling and heightened mitogen-activated protein kinases – endothelin-1 (ET-1) signaling [18].

VSMCs are the predominant cell type found in the arterial wall and are essential for the structural and functional integrity of the vessel. VSMCs are also a target of insulin action and are affected by insulin resistance as discussed for ECs. Insulin-induced vasodilation in VSMCs is mediated by metabolic signaling, which includes IRS-1/PI3K and cyclic guanosine monophosphate (cGMP) signaling pathways. This signaling leads to a reduction of free intracellular calcium and reductions in calcium sensitivity [19]. It is known that VSMCs can differentiate from a quiescent, contractile phenotype to a proliferative, synthetic phenotype following arterial injury and in atherosclerotic diseases [20]. Indeed, VSMCs are capable of osteoblast transdifferentiation in calcifying arteries [21]. Increased reactive oxygen species (ROS) production leads to the activation of redox-sensitive proinflammatory transcription factors, such as NF-κB and transcription factor runt-related transcription factor 2, and further results in the phenotypic switch of VSMCs into osteoblast-like cells [22]. It has been reported that angiotensin II (Ang II) exacerbated vascular calcification through activation of the transcription factors, runt-related transcription factor 2 and NF-κB, regulation of matrix Gla protein, and inflammatory cytokines expression in human VSMCs [23]. Thus, advancements in our understanding of the cellular and molecular mechanisms in vascular calcification should provide a viable target for an antivascular stiffening strategy.

Adaptive Immunity, Inflammation Response, and Oxidation Stress in AS

Inflammation cytokines, such as p-selectin, thrombomodulin, intercellular adhesion molecules 1, cytokine C-reactive protein, serum amyloid A, interleukin 6 (IL-6), IL-8, tumor necrosis factor-α (TNF-α), and intercellular adhesion molecule 1 are associated with endothelial dysfunction in AS [24]. Recently, it has been recognized that the adaptive immune system is important in the genesis of AS. Specifically, T lymphocytes, a population of immune cells, have been identified in the artery walls. Activated T cells can be subtyped according to their cytokine profile. T helper 1 cells secrete IL-2, TNF-β, and interferon, whereas Th2 cells typically produce IL-4, -5, -6, and -10 [25]. Increased T helper secretion of cytokines, chemokines, and growth factors leads to an inflammatory process and may lead to fragmentation of elastic membranes and destruction of cell-protective matrix layers. However, CD4$^+$CD25$^+$Foxp3$^+$ regulatory T cells (Tregs) can protect the proinflammatory activation of vascular cells. The mechanisms by which Tregs protect against inflammation are thought to be mediated, at least in part, by directing cell-to-cell interactions as well as through the secretion of soluble anti-inflammatory cytokines, including IL-10 and transforming growth factor-β [26].

Oxidative stress has been linked to an increased prevalence of AS in diabetes mellitus, hypertension, and hypercholesterolemia. Excess oxidant burden alters DNA transcription, leading to cellular proliferation and interruption of numerous redox sensitive signaling pathways that influence arterial remodeling [27]. The generation of ROS is required for normal cell signaling and physiological responses. Recently, it was shown that prolonged exposure to increased mitochondrial oxidative stress decreased aortic compliance and induced cardiac dysfunction [28]. Specifically, the data elucidated the significance of

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lifelong superoxide dismutase 2 deficiency on the phenotype, function, and molecular signaling pathways in aortic SMCs. These results further showed how oxidative stress promotes AS by inducing vascular wall remodeling, intrinsic changes in SMC stiffness, and aortic SMC apoptosis [28]. The link between oxidative stress and AS offers new clues to identify vascular dysfunction and may allow for development of novel targeted therapeutic interventions.

Advanced Glycation End Products, Collagen, and Elastin in Vascular Stiffening

The association between advanced glycation end products (AGEs) and AS was found in the elderly and patients with CRS [29]. Indeed, AS is characterized by decreased turnover of collagen and elastin and increased AGEs and extracellular matrix (ECM) cross-links. Elastic fibers undergo lysis and disorganization subsequent to their replacement by collagen and other matrix components. These events cause the loss of elasticity and induce stiffening [29]. Studies have investigated the susceptibility of elastin to glycation and subsequent changes in its physicochemical properties [30]. Thus, AGEs enhance collagen content and induce changes in mechanical properties of the conjunctive tissue by conferring a high resistance to enzymatic proteolysis, decreasing their rate of degradation, increasing the production of ECM, and creating the cross-linking of the extracellular proteins. In the context of vascular stiffening, matrix metalloproteinase (MMPs) are involved in the regulation of the structural integrity of the ECM. Recently, it was reported that in the arterial vasculature from CKD patients, the presence of diabetes markedly upregulated MMP-2 and -9, and this adaption is strongly associated with elastic fiber degradation, AS, and calcification. The increase in MMPs in diabetic vessels was also accompanied by pronounced generation of angiostatin, and the reduction of microvascular density was associated with impaired vasorelaxation [31]. These data confirm that MMPs are upregulated in the arterial vasculature in patients with CVD and CKD.

The Renin Angiotensin Aldosterone System in AS

Ang II and aldosterone are two hormones that contribute significantly to AS [1]. There is evidence that the activation of the renin angiotensin aldosterone system (RAAS) plays an important role in the pathogenesis of AS and vascular calcification. In the course of RAAS-induced vascular injury, Ang II binds to its type 1 receptor to induce oxidative stress, mainly mediated by NADPH oxidase. In addition to a systemic response of heightened RAAS activation in obesity contributed by hepatic and adipose tissue angiotensinogen [2], and increased adrenal aldosterone production by adipose tissue derived factors, local activation of RAAS in the vascular tissue is seen in obesity and diabetes [1]. Both hormones directly modulate AS and one of the mechanisms involves impaired bioavailability of NO though activation of NADPH oxidase, thereby promoting oxidative stress and decreased NO bioavailability [7]. Aldosterone also increases epithelial Na^+ channel expression on the EC surface associated with increased cortical stiffness of the cytoskeleton [1]. Accumulating evidence also suggests the role of inappropriate activation of RAAS in causing impairment of T regulator immune cell function [2]. Adoptive transfer of Tregs prevented enhanced vascular injury and AS after Ang II and aldosterone infusion. Moreover, suppression of NADPH oxidase activation in vascular cells by secretion of IL-10 from Tregs [7] suggests a role of immune mediated regulation of vascular oxidative stress and AS.

Activation of RAAS may also cause insulin resistance that in turn may contribute to impaired metabolic insulin signaling and bioavailability of NO. In this regard, mTOR/S6 kinase, an important kinase that is responsible for the phosphorylation of serine residues in the IRS-1 is activated by both Ang II and aldosterone [2]. The role of Ang II and aldosterone modulation in insulin signaling has been reported in VSMC [7]. Some of our studies confirmed

a critical role for Ang II signaling through its type 1 receptor in conjunction with an altered redox-mediating impaired endothelial, cardiac and renal function in the CRS [32]. Our recent studies have further explored the signaling pathways by which enhanced tissue RAAS contributed to insulin resistance in cardiovascular tissue. We concluded that the activation of mTOR/p70S6K by Ang II in the vascular endothelium may contribute to the impairment of insulin-stimulated vasodilation through phosphorylation of IRS-1 [33]. Thus, one aspect of potential importance in our studies is that the increase in EC stiffness was associated with a reduced release of NO. Moreover, cross-talk between Ang II and aldosterone signaling underscores the importance of Ang II-aldosterone interactions in the development of insulin resistance, vascular dysfunction and AS.

Transglutaminase in AS

Tissue transglutaminase (TG2) is a multifunctional protein that plays a key role in AS. It presents in significant amounts in the vasculature and stabilizes the ECM through cross-linking. TG2 represents a link between insulin resistance and AS due to its regulation of NO availability. Impaired bioavailability of NO is accompanied by impaired S-nitrosylation of TG2, increased TG2 secretion to the cell surface and ECM and enhanced cross-linking activity in the vasculature [34]. Moreover, vascular smooth muscle cytoskeletal proteins mediated by AS are also substrates of TG2 [34]. TG2 is also involved in the inward remodeling of the resistance arteries, and this process requires actin dynamics and alterations in actin cytoskeletal structures. Recently, an increased vascular TG2 activity was associated with AS in high-fat fed mice that preceded hypertension [35], thereby suggesting activation of TG2 and AS as an early event in the long-term effects of obesity on the vasculature. In this regard, activation of TG2 caused by cytokines, including TNF-α [35], and RAAS [36] in CRS may result in insulin resistance, decreased bioavailability of NO and AS.

AS Associates with CVD Arising and Progression

Richard Bright, generally regarded as the 'father of nephrology', was the first one to postulate in 1827 that systemic arterial changes might be responsible for the link between diseased kidney and LVH. He described a case: 'we again distinctly trace the existence of a highly diseased condition of the kidney, coupled with the excretion of albuminous urine. The enlarged state of the heart seems to be bespoke some cause of obstruction to the circulation through the system beyond what we discovered, nor will I venture to say what share this might have had in giving rise to the dropsy' [37]. Thus, stiffness of the aorta and its primary branches are implicated in the development of coronary artery disease (CAD). Stiffening of central arteries increases systolic pressure, decreases diastolic pressure, resulting in an increased pulse pressure and PWV. On one hand, the increased systolic pressure increases cardiac afterload, LV mass, and oxygen demand. On other hand, the decrease in diastolic pressure can reduce coronary blood flow during the diastole. These changes can result in LV remodeling and thereby cause LVDD and development of CAD (fig. 1) [38].

LVH may have a significant influence on the relationship between PWV and LV diastolic function. Although the physiology of diastolic function is complex, the intrinsic LV abnormalities contributing to LVDD are impaired in LV relaxation, increased LV asynchrony, and the complex of LVH [39]. LVH increases the ratio of myocardial mass to volume, and the degree of hypertrophy is the main determinant of chamber stiffness. LVH often leads to poor LV compliance and a vicious cycle of greater LV filling pressures and hypertrophy [39]. Furthermore, LVDD in hypertrophied hearts contributes to HF with preserved ejection, which

consists of prolonged isovolumic LV relaxation, slow LV filling, and increased diastolic LV stiffness [40]. A characteristic feature of HF with preserved ejection is slow LV relaxation, which may reduce LV stroke volume, especially at high heart rates [38]. LV relaxation is dependent on both cross-bridge detachment and sarcoplasmic reticular Ca^{2+} reuptake [40]. Endothelial dysfunction and NO signaling are involved in this regulation since NO diffuses into the cardiomyocytes and interacts with soluble guanylate cyclase. NO stimulates the soluble guanylate cyclase to generate the second messenger cGMP from GTP. The soluble cGMP activates the cyclic nucleotide-dependent protein kinase G [41]. Protein kinase G, a kinase involved in phosphorylating a number of proteins, regulates Ca^{2+} concentrations and sensitization, hyperpolarizes the cell through potassium channels, and causes actin filament and myosin dynamic alterations, and subsequently results in cardiomyocyte relaxation [42]. Thus, these changes occur to some extent with aging and may be particularly prominent in AS patients with cardiac hypertrophy in whom HF symptoms develop despite having a preserved ejection fraction.

Interaction of AS and Kidney Diseases

Vascular pathologies including atherosclerosis, arteriosclerosis, calcifications, and vascular remodeling are involved in AS in inpatients with CKD. In contrast, an increase in AS leads to a rise of the PWV, which increases the afterload and induces LVH and vascular damage within the kidney (fig. 1).

AS Affects Kidney Function

Urinary albumin excretion has long been thought to be not only a membrane barrier defect comprised of podocytes, glomerular-based membrane, and the vascular endothelium but also the presence of generalized vascular disease [43]. Early signs of renal damage, such as microalbuminuria, mildly decreased GFR, and increased renal vascular impedance, are relatively common conditions in patients with AS [44]. For example, diabetes, a powerful risk factor for CVD, is a major risk factor for albuminuria and reduced GFR. Diabetes is initially associated with generalized hyperperfusion and microvascular hypertension and is also associated with increased AS [7]. As noted above, increased AS is associated with an increase in the amplitudes of the forward and reflected pressure waves and is therefore associated with CKD [44]. Indeed, renal circulation is unique with respect to transmitted blood pressure fluctuations [45]. Although the microcirculation of other organs is protected by the high resistance of the precapillary arterioles, the renal afferent arterioles provide relatively low resistance. This permits transmission of hydrostatic pressure to the glomerular filtration barrier, producing a high glomerular filtration fraction. This renders the glomerulus susceptible to pressure related damage since elevated pressure pulsatility leads to increased afferent arteriolar tone with associated reduction in the filtration fraction. Meanwhile, compensatory changes occur via tubuloglomerular feedback with RAAS activation, resulting in efferent arteriolar vasoconstriction to maintain glomerular filtration. Furthermore, Ang II may cause pressure-induced renal injury via its ability to induce systemic and glomerular hypertension or cause ischemia-induced renal injury secondary to intrarenal vasoconstriction and decreased renal blood flow [46]. Ang II may also cause tubular injury secondary to angiotensin-induced proteinuria. Ang II also activates renal fibroblasts to become myofibroblasts, stimulates the production of the profibrotic cytokine transforming growth factor-β, induces oxidative stress, and stimulates chemokines and osteopontin that may cause local inflammation, and stimulates vascular and meningeal cell proliferation and hypertrophy [2]. Thus, loss of effective renal

autoregulation contributes to glomerular hypertrophy, glomerular-based membrane injury, and subsequent excess ECM production and glomerulosclerosis with permanent reduction in GFR.

Deterioration in Renal Function Is Associated with Increased AS

CKD affects 10–13% of the population in the US and is associated with a dramatically increased CVD mortality, which increases with severity of renal impairment. This excess CVD risk is in part attributed to an increase of traditional risk factors among people with CKD but may also relate to the complex metabolic and vascular changes of CKD, including AS [45]. A number of studies among patients with CKD have shown an independent cross-sectional relationship between aortic PWV and renal function [47]. Several reasons can be advanced for the progressive AS in patients with CKD. First, accumulation of AGEs affecting vessel wall matrix occurs in patients with CKD and may be related to AS [29]. Second, a significant component of the morphological and structural changes during renal remodeling involves alterations in collagen content and composition in CKD. Collagen fibers, mainly types I and III, represent the more rigid components of the arterial wall and also contribute to the development of renal fibrosis. In both kidney and arteries, Ang II and aldosterone participate in collagen accumulation and are known to be prevented by converting enzyme inhibition and aldosterone antagonism [1]. Third, vascular calcification promotes AS and occurs in CKD as a result of disordered calcium, phosphorous and vitamin D metabolism, secondary hyperparathyroidism and changes in factors such as fibroblast growth factor 23 and fetin A [48]. Fourth, uric acid may accelerate AS development. Mechanisms implicated for increased AS in patients with uricemia include chronic fluid overload, arterial calcifications, inflammation, sympathetic nervous system overactivity, activation of RAAS, increased lipid oxidation, and abnormalities in the NO system [49]. Thus, this bidirectionality between kidney disease and AS sets up a potentially vicious cycle, wherein a primary abnormality in either aorta or kidney function could lead to accelerated deterioration in the structure and function of both organs.

Sex Difference in the Relationship between AS and LV Diastolic Function

It is known that substantial differences in arterial and ventricular stiffness exist between men and women, with greater stiffness described in women compared to age-matched men [50]. Differences between men and women in central hemodynamics and AS have been described in previous studies and have been partially ascribed to differences in hormonal factors, endothelial function, height, aortic wall dimensions, and heart rate [50]. Consistent with other studies, our investigative group reported that there is a gender difference in myocardial stiffness and diastolic dysfunction and that these differences contribute to development of the CRS in mice fed a Western diet high in fat and fructose [51]. Indeed, the rates of development of CVD related to CRS, such as diastolic dysfunction, coronary vascular stiffness and impaired vasorelaxation are different in males and females. Normally women develop CVD approximately 10 years later than men, but women show a marked increase in CVD in the postmenopausal period [52]. The increased risk of CVD in postmenopausal women has been linked to the decrease in plasma estrogen levels since estrogen may provide benefit to premenopausal women. Especially, women in postmenopause are more susceptible to the deleterious effects of diastolic ventricular-vascular coupling [53]. A consistent finding among population studies is that women significantly outpace men in this disease in a range of 2:1 [54]. The female heart will tend to show a concentric hypertrophy, which is associated with an increase in wall thickness and initial preservation of cavity size and ejection fraction, while the male heart tends to develop a more eccentric hypertrophy, which is associated with

progressive LV dilation and dysfunction. These differences between men and women are widely held to be related to sex hormones such as estrogen on the vasculature and the myocardium [53]. Thus, women display increased arterial and ventricular stiffening and deranged ventricular-arterial coupling compared to men, particularly with aging. This may impair cardiac performance in the presence of normal ejection fraction by increasing blood pressure liability, reducing cardiac efficiency, prolonging diastolic relaxation and increasing diastolic chamber stiffness [55].

Sex differences in the arterial and ventricular stiffening have mainly been attributed to the effects of estrogen which are primarily mediated by estrogen receptor (ER) α, ERβ, and G-protein coupled receptor 30. ERs and G-protein coupled receptor 30 are expressed in ECs, VSMCs, and cardiomyocytes [56]. Estrogen may promote endothelium-dependent vasodilation by increasing the releases of NO, prostacyclin, and endothelium-derived hyperpolarizing factor. In comparison, estrogen decreases the release of ET-1 and Ang II, which are potent vasoconstrictors and procoagulants [57]. Meanwhile, estrogen can decrease the sympathetic activity, circulating levels of norepinephrine, collagen synthesis, and RAAS [58]. Furthermore, estrogen is suggested to protect against development of the CRS and the prevalence of obesity, insulin resistance, and type 2 diabetes increases in postmenopausal women [59]. The mechanisms in estrogen-induced endothelial nitric oxide synthase (eNOS) activation and NO expression are that estrogen activates PI3K/Akt pathways, which leads to phosphorylation and activation of eNOS and increases the NO production [60]. Estrogen also increases eNOS activity by causing rapid ERs-dependent activation of mitogen-activated protein kinases [60]. Thus, estrogen plays important roles in maintaining cardiovascular and kidney function.

Conclusion

It is well known that AS is significantly associated with all-cause mortality and the occurrence of CVD events and that it conditions the outcome of patients with CKD (fig. 1). These research results bring us new concepts on the interactions between AS, vascular resistance and wave reflections, and final end-organ damage in the heart and kidney. Such an approach should help in establishing new goals in the reduction of cardiovascular risk that is distinct from atherosclerosis. Although AS and PWV provide useful prognostic information concerning CVD events in different populations, future studies should further confirm that a reduction in PWV is indeed associated with a concomitant reduction in CVD events, independent of other risk factor control, such as in the reduction of blood pressure, glycaemia, and lipids. Thus, additional studies with a well-controlled and well-designed clinical trial remain important.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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