Increased Aortic Stiffness: An Unfavorable Cardiorenal Connection

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Despite the many potentially life-threatening complications that can accompany renal disease, cardiovascular disease (CVD) remains the leading cause of death in these patients. Patients with renal dysfunction have more cardiovascular events at an earlier age and they tolerate these events poorly.\(^1,2\) Established renal disease is associated with increased aortic stiffness and left ventricular (LV) hypertrophy, which are two important risk factors for CVD events. Conversely, aortic stiffness and LV mass have been related to each other and to early signs of renal damage, such as microalbuminuria.\(^3,4\) There are several potential explanations for this 3-way interrelationship between cardiac, aortic, and renal function. These organs share several increasingly prevalent risk factors, including advanced age, hypertension, and diabetes, which may contribute to a parallel deterioration in function. Alternatively, dysfunction in one organ may damage the others. Unfortunately, our understanding of these complex interrelationships is currently limited.

The arterial and renal components of the cardio-aorto-renal ménage au trois are highlighted in a review by Safar et al in this issue of Hypertension.\(^5\) In work that has spanned nearly 3 decades, Professor Safar and colleagues have contributed immeasurably to our understanding of the role of abnormal arterial function in renal disease. As detailed in the review, they have shown that after accounting for common risk factors, increased arterial stiffness is present at various stages of renal dysfunction and represents a grave prognostic indicator. In an end-stage renal disease cohort, they demonstrated that arterial wall stiffness was an independent predictor of all-cause and cardiovascular mortality and that failure of arterial stiffness to improve after an intervention that lowered blood pressure was also associated with increased total mortality. Conversely, they found that serum creatinine on an index examination is associated with increased arterial stiffness in a cross-sectional analysis and is an independent predictor of further arterial stiffening when evaluated prospectively. However, as detailed in the review, many aspects of the relationship between arterial stiffness and renal dysfunction and the effects on the heart remain incompletely understood.

What Is Arterial Stiffness?
The term “arterial stiffness” is widely used and has been variably defined. To decide which stiffness measures best characterize arterial function, it helps to consider why arterial stiffness is important. Arteries serve a dual role of conducting blood to the peripheral tissues and buffering the pressure pulsations that are a necessary accomplishment of intermittent ventricular pumping. Loss of this buffering function manifests as elevated pulse pressure, which adds to load on the heart and likely damages the large and small vessels as well. Pulse pressure may be increased because of a larger forward pressure wave or an earlier or larger wave reflection. Therefore, two important functional stiffness measures that should be evaluated are impedance to pulsatile flow (characteristic impedance), which determines the size of the pressure wave produced by a given flow wave, and pulse wave velocity, which determines how fast waves travel to reflecting sites and back.\(^6\) In terms of regional arterial function, stiffening in the central (elastic) aorta accounts for most of the increase in pulse pressure that is seen with aging and in various disease states, such as hypertension.\(^6\) Therefore, aortic characteristic impedance and carotid–femoral pulse wave velocity are two key variables that should be assessed.

Potential Effects of Aortic Stiffening on Renal Function
Aortic stiffness is of particular importance to the kidney because of the unique structure of the renal microcirculation. Microvessels in tissues such as heart, brain, skin, or skeletal muscle include precapillary arterioles and metarterioles that provide \(\approx 75\%\) of the series resistance of the bed and therefore dissipate most of the mean and pulsatile energy content of the advancing pressure and flow waveform before it reaches the capillary. In contrast, glomerular capillaries are positioned between afferent and efferent arterioles. Because efferent arteriolar resistance is normally greater than afferent resistance, the pressure drop across the afferent arteriole is relatively low, so mean and pulsatile pressures in the glomerulus are relatively high (\(\approx 60\%\) of arterial values). This increased level of hydrostatic pressure maintains a high glomerular filtration fraction, which is normally \(\approx 20\%\) of renal plasma flow but exposes the glomerular capillary to potentially damaging pulsatile pressures if aortic stiffness and pulse pressure are elevated.
The kidney normally autoregulates blood flow and glomerular filtration rate (GFR) across a wide range of perfusion pressures. The combination of myogenic tone in the afferent arteriole and tubuloglomerular feedback (TGF), which modulates tone in afferent and efferent arterioles, mediates the bulk of this autoregulation, which has traditionally been defined in terms of mean arterial pressure. However, recent studies have shown that myogenic tone in the afferent arteriole is affected by pressure pulsatility. Therefore, if pulse pressure rises out of proportion to mean pressure, renal vascular resistance will rise and renal blood flow will fall. This blood pressure pattern is commonly observed with advancing age beyond the fifth decade and may provide a hemodynamic mechanism for an age-related decline in renal blood flow and GFR. TGF may normally offset a component of any pulse pressure-related increase in afferent arteriolar tone while also increasing efferent arteriolar tone directly and through activation of the renin-angiotensin-aldosterone system (RAAS). However, activation of the RAAS may adversely impact aortic and ventricular structure and function, leading to a vicious cycle. Furthermore, a TGF-mediated increase in GFR comes at the expense of restoring some of the excessive pressure pulsatility in the glomerulus, leading to a compromise between conflicting goals of attenuating pulsatile pressure exposure in the glomerulus while maintaining GFR. Clearly, this highly speculative chain of events needs to be evaluated in appropriate models.

A long-term increase in pulse pressure with or without an increase in afferent arteriolar tone also results in higher than normal dissipation of pulsatile energy in the microcirculation of the kidney (and elsewhere). This biophysical stimulus has been shown to trigger upregulation of many mechanosensitive genes and may result in long-term remodeling of the renal microcirculation. In summary, glomerular dysfunction, remodeling, or loss created by the foregoing mechanisms may underlie the association between elevated pulse pressure and reduced renal function and may partially explain why pulse pressure is a strong independent predictor of microalbuminuria and progressive nephropathy.

### Renal Dysfunction May Adversely Affect Aortic Function

Conversely, there are several potential mechanisms for aortic stiffening and dysfunction secondary to renal insufficiency. As noted in the Safar review, abnormalities in endothelial function, oxidative stress, and electrolytes and activation of the RAAS are often present and may contribute to impaired aortic function in patients with renal dysfunction. Aortic calcification is common in patients with renal dysfunction, although it is less clear whether this calcification increases aortic stiffness directly or represents a marker for aortic dysfunction. A reciprocal relationship between bone resorption and aortic calcification is evident in animal models and in humans. Mediators of calcium and bone homeostasis, including osteoprotegerin and various bone morphogenetic proteins, may play a role in normal arterial function and in the process of calcium deposition in the aortic wall. Alternatively, several of the calcium/bone regulatory hormones, including parathyroid hormone, parathyroid hormone-related peptide, and calcitonin/calcitonin gene-related peptide, have direct effects on vascular tone and could affect aortic stiffness measures, such as characteristic impedance, because the latter is highly sensitive to diameter.

### Implications and Perspective

Regardless of the pathogenesis of increased aortic stiffness in patients with renal dysfunction, there are many reasons why the combination is particularly deleterious. Aortic stiffness and premature wave reflection are associated with concentric left ventricular hypertrophy and abnormal diastolic relaxation, which may give rise to the syndrome of heart failure with preserved left ventricular systolic function. Renal dysfunction is commonly associated with volume lability and overload. Clearly, this combination can present a management challenge, particularly in patients with end-stage renal disease on dialysis who may manifest a narrow homeostatic window between volume-related hypotension and pulmonary edema. Increased aortic stiffness and diminished renal function are both associated with increased risk for coronary artery disease, adding to the propensity for catastrophic cardiovascular events and poor outcomes.

Future research should focus on unraveling the foregoing interrelationships between cardiac, aortic, and renal function. Additional data are needed that evaluate the relationship between renal function and aortic stiffness in unbiased community-based samples. Future studies should include a direct assessment of GFR, rather than using regression-based approaches. The latter formulas include terms for age, weight, and gender, which are important and potentially confounding determinants of aortic stiffness. Aortic stiffness should also be measured directly and the focus should probably be on central aortic properties (characteristic impedance and carotid-femoral pulse wave velocity). The role of microvascular remodeling in the kidney (and elsewhere in the body) and the relationship of this process to aortic stiffening and pulsatile load should be investigated. Gross changes in kidney structure and volume, as assessed by computerized tomography or MRI, may also provide clues to the deleterious effects of abnormal cardio-aorto-renal coupling. Finally, a number of known and emerging biomarkers, including markers/mediators of RAAS activation, inflammation, oxidative stress, protein glycation, bone mineralization, and calcium metabolism and natriuretic peptides, may provide mechanistic and prognostic insights. Novel animal models of increased large artery stiffness are needed to prospectively evaluate the effects of increased pulsatile load on renal function during the life of the animal. A more thorough characterization of large and small artery structure and function in the subtotal nephrectomy model is needed. Finally, a better understanding of the effects of various classes of drugs on large artery stiffness and intra-renal hemodynamics may enhance our ability to successfully intervene in the vicious cycle of aortic stiffening and progressive renal dysfunction and soften the unfavorable aortic “connection” that the French have so eloquently exposed.

### References


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