

Editorial

## “Stiff Central Arteries” Syndrome: Does A Weak Heart Really Stiff the Kidney?



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Renal impairment is common in heart failure, with the prevalence of chronic kidney disease (CKD) estimated to be approximately 30% in patients who have chronic heart failure. Several studies have demonstrated that CKD is associated with increased mortality and rehospitalization in heart failure. Worsening renal function, defined as an increase in serum creatinine  $\geq 0.2$  mg/dL or a corresponding decrease in estimated glomerular filtration rate  $\geq 5$  mL  $\times$  min  $\times$  1.73 m<sup>2</sup>, occurs in approximately 25% of patients who have heart failure (HF) and predicts substantially higher morbidity in HF [1]. In one meta-analysis, 63% of heart failure patients had any renal impairment, and 29% had moderate to severe insufficiency [2]. After adjusting for other factors, these investigators found that all-cause mortality was increased for patients who had any impairment (hazard ratio [HR] = 1.56; 95% confidence interval [CI] 1.53 to 1.60,  $P < .001$ ) and moderate to severe impairment (HR = 2.31; 95% CI 2.18 to 2.44,  $P < .001$ ). Mortality worsened incrementally across the range of renal function, with a 15% (95% CI 14% to 17%) increase in risk for every

0.5 mg/dL increase in creatinine and a 7% (95% CI 4% to 10%) increase in risk for every 10 mL/min decrease in eGFR. The pathogenesis of renal dysfunction in HF is poorly understood and difficult to define because its mechanism is complex and multifactorial in most instances.

Heart failure is increasingly associated with aging and accompanied by stiffening of the arterial system, particularly the central larger arteries including the aorta and renal arteries [3,4]. Progressive aortic stiffness with aging is evidenced by a twofold increase in aortic pulse velocity between the ages of 20 and 80 (Fig. 1) [5]. These changes are amplified by the early return of the reflected pressure wave in peripheral arterioles. Therefore, input impedance at the level of the ascending aorta is quadrupled—a twofold increase in aortic impedance is doubled again by the early return of the pressure wave reflection. As a consequence, for the same ejection flow, the pulse pressure in the aorta and central arteries is quadrupled. Although the brachial pulse pressure also increases with age, it does not completely reflect this increase in central pulse pressure

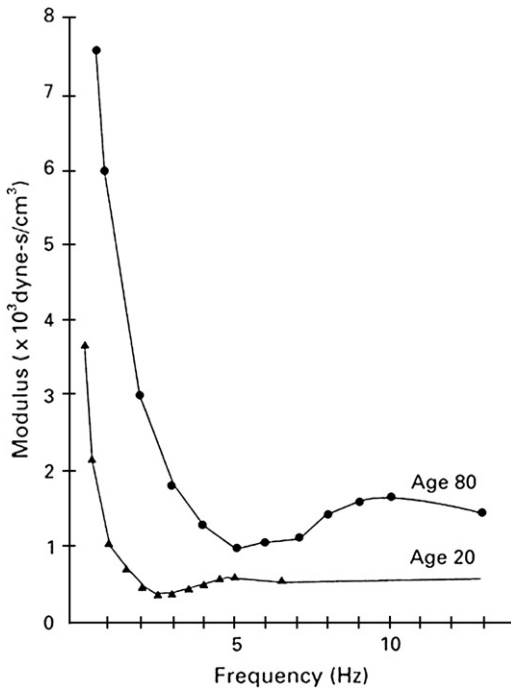


Fig. 1. Estimated ascending aortic impedance modulus in typical 20-year-old and typical 80-year-old human subjects, based on twofold increase in aortic characteristic impedance and in aortic pulse wave velocity. Modulus of impedance at heart rate frequency (1 to 3 Hz) is increased by more than fourfold. (From Nichols WW, O'Rourke MF, McDonald DA. McDonald's blood flow in arteries: theoretical, experimental and clinical principles. 5th edition. London and New York: Hodder Arnold; 2005. Copyright © 2005. Reproduced by permission of Edward Arnold [Publishers] Ltd.)

(Fig. 2). This increase in arterial pulse pressure has minimal effect on most tissues and organs because their flow is determined by mean pressure as these cells are protected by a reflex constriction of the arterioles and arteries upstream. The inability of these larger blood vessels to vasoconstrict as much (proportionately) means that the downstream organs are exposed to higher pulsatile circumferential and longitudinal stress, which is associated with a fourfold increase in arterial pressure [6]. The ability of the kidneys to withstand these increases in pulse pressure is impaired in aging and diabetes. Aging changes in large arteries lay the groundwork for the development of small vessel arterial disease [6,7]. The damage to small arteries induced by increased pulsatile stress has been shown to result in disruption of their endothelial and smooth muscle cells with consequent architectural disarray of the vessel. These changes

result in small arterial dilations and aneurysms seen in the kidneys of patients who have hypertensive disease [4]. It has been shown that these changes are largely reversible when disrupting forces are reduced [7]. Medications such as angiotensin converting enzyme (ACE) inhibitors that reduce arterial stiffening and decrease stress on renal microvessels have been shown to delay progress of renal disease [8].

Arterial stiffness is also a risk factor for HF [9]. The increase in arterial stiffness associated with age or hypertension, as evidenced by increases in the speed and magnitude of reflected waves, amplifies systolic pressure and thus increases the load on the left ventricle [10–12]. This interplay between vascular and ventricular stiffening may lead to load-dependent impairment of systolic as well as diastolic function [13]. Using a combination of carotid ultrasound and cardiovascular MRI tissue tagging in 1100 asymptomatic subjects, the Multi-Ethnic Study of Atherosclerosis (MESA) investigators [14] found a significant association between arterial compliance and circumferential systolic strain rates in all myocardial regions ( $P < .05$ ) and with diastolic strain rates in the lateral and septal wall regions ( $P < .05$ ). With the use of multiple linear regression analyses, a direct linear relationship between carotid artery distensibility coefficient and circumferential systolic strain rates was demonstrated across all left ventricular segments and slices, even after adjustment for left ventricular mass and cardiovascular risk factors. Using regression analyses, the MESA investigators also found a significant relationship between arterial compliance and diastolic strain rates in the septal and antero-apical walls. They noted that this relationship remains significant even after adjustment for multiple variables. These findings suggest that central arterial stiffness and impaired regional left ventricular function are present in asymptomatic patients even in the absence of cardiac hypertrophy [15].

The function of the kidney, or the glomerular filtration rate (GFR), depends on several factors, including hydrostatic pressure gradients, oncotic pressure, and permeability of glomerular basement membrane. Hydrostatic pressure depends on the pressure differential between the afferent and efferent arterioles and cardiac output. In a normal individual, about one fifth of the cardiac output is directed towards the kidneys; therefore, cardiac function has a major impact on the hydrostatic pressure in the kidneys. Renal function is also influenced by neurohormonal modulators,

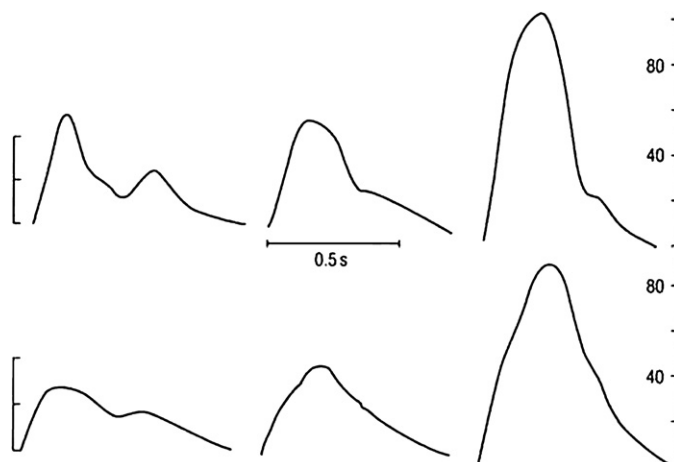


Fig. 2. Change in amplitude and contour of the upper limb (*top*) and ascending aortic (*bottom*) pressure wave with age, as recorded in 3 female members from the same family at age 18 (*left*), at age 48 (*center*), and 97 years (*right*). Pressure calibration in mm Hg. Upper limb pulse pressure was just more than twice as high in the old subject compared with the young subject (102 of 46 mm Hg), whereas aortic pulse pressure was almost four times higher (104 of 27 mm Hg). (From Nichols WW, O'Rourke MF, McDonald DA. McDonald's blood flow in arteries: theoretical, experimental and clinical principles. 5th edition. London and New York: Hodder Arnold; 2005. Copyright © 2005. Reproduced by permission of Edward Arnold [Publishers] Ltd.)

including the renin-angiotensin-aldosterone system, natriuretic peptides, arginine vasopressin, and endothelins. Finally, the intrinsic autoregulatory mechanism of the kidneys also tightly controls GFR. In HF, both hydrostatic pressure gradients and oncotic pressure are impaired, resulting in fluid and sodium retention. The loss of pulsatility in the descending aorta and the renal arteries results in impairment of renal hemodynamics and consequently kidney function, including the GFR. In addition, stiff systemic arteries result in systemic hypertension that in turn results in kidney damage.

Stiff arteries, therefore, cause both cardiac and renal dysfunction. In patients with stiffening of the central arteries and combined organ dysfunction, worsening of left ventricular contractility results in impaired hydrostatic pressure in the kidneys, which consequently reduces GFR. The initial injury, therefore, is the stiffening of the arteries; left ventricular dysfunction is one factor that adds insult to this injury. One could argue that stiffening of the arteries “stiffs” both the heart and the kidneys, and that left ventricular dysfunction and renal dysfunction are only the end-game in this sequence of events. Worsening left ventricular systolic function in individuals with renal dysfunction due to central aortic stiffening only exacerbates the cardiorenal syndrome, or rather, the “stiff central arteries syndrome.”

“Destiffening” agents (Table 1), therefore, should ameliorate both heart and kidney damage. The findings of the ongoing National Institutes of Health (NIH)-sponsored RELAX trial, which is investigating the role of one destiffening agent, chronic PDE5 inhibition versus sildenafil, on ventricular hypertrophy and exercise performance, should provide important data on the

Table 1  
Arterial destiffening strategies

Reduce smooth muscle tone
Nitrates, ACE inhibitors, ARBs, calcium channel blockers
Enhance endothelial function/relaxation
Exercise
Antioxidants
Tetrahydrobiopterin
Statins
Rho kinase inhibitors
Alter structural properties
Reduce fibrosis (ARBs, aldosterone blockers, TGF- $\beta$ 1 inhibitors)
Limit or reverse hypertrophy
Advanced glycation end-product cleavage
Enhance elasticity (elastin, fibrillin, etc)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; TGF, transforming growth factor.

Data from Kass DA. Ventricular arterial stiffening: integrating the pathophysiology. Hypertension 2005;46(1):185–93.

management and pathogenesis of the cardiorenal syndrome [12].

In this issue, Dr. George Bakris has assembled a stellar panel of contributors who touch upon several other elegant mechanisms that contribute to the pathogenesis of the cardio-renal syndrome. The importance of understanding these issues and concepts cannot be overemphasized, since the negative impact of renal insufficiency in heart failure is profound.

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