Arterial Stiffness and Hypertension
A Two-Way Street?

Stanley S. Franklin

Elastic artery stiffening, an age-related process, can be accelerated in the presence of hypertension. Hypertension may produce arterial stiffening by both functional and structural mechanisms. Acute and potentially reversible stiffening of the thoracic aorta and its branches occurs with an increase in arterial blood pressure (BP). Young adult hypertensive subjects have a “downstream” increase in resistance at the level of the arterioles, causing an “upstream” increase in transmural pressure at the level of the central elastic arteries; this causes weight-bearing elastic lamellae of the large arteries to stretch and become stiffer. Elevated BP over time can lead to vascular remodeling, hypertrophy, and hyperplasia—structural changes that produce intrinsic arterial stiffening. This form of hypertension in young adults typically presents with elevated diastolic BP in the subtypes of systolic–diastolic or isolated diastolic hypertension. In contrast, isolated systolic hypertension of the elderly, associated with increased systolic BP and decreased diastolic BP, typically presents with widened pulse pressure (PP) as a marker of increased arterial stiffness. The arterial stiffness seen in elderly persons with isolated systolic hypertension is characterized by fissuring and fracturing of the elastin protein, collagen proliferation, and calcium deposition, frequently associated with a widened and tortuous aorta. As large arteries dilate, wall tension and pulsatile stresses increase and exacerbate artery wall degeneration, thus initiating a positive feedback whereby increased hypertension leads to further degeneration.

The Framingham Heart study showed that untreated hypertension may accelerate the rate of large artery stiffness and thus perpetuate a vicious cycle of accelerated hypertension and further increases in large artery stiffness. Middle-aged and elderly persons with untreated hypertension were more likely to present with an age-related marked increase in systolic BP and decrease in diastolic BP as compared with their normotensive counterparts. These findings were confirmed by Benetos et al, who found that annual rates of progression in pulse wave velocity (PWV) were higher in treated hypertensive subjects than in normotensive subjects, suggesting accelerated progression of arterial stiffness among the treated hypertensive subjects. In addition, these investigators showed that mean arterial pressure, a surrogate measure of peripheral resistance, did not increase throughout the 6-year follow-up, but PWV progression was 3-times greater in the poorly controlled as compared with the well-controlled hypertensive subjects. Therefore, the Framingham and Benetos et al studies suggest a linkage between incompletely treated or untreated hypertension and subsequent acceleration of age-related large artery stiffness—a measure of vascular aging.

The conventional wisdom, as presented, is that arterial stiffness is the result of hypertension rather than its cause, but there is now evidence that the relationship between hypertension and arterial stiffness may be bi-directional. In 1999, Liao et al in the Atherosclerosis Risk In Communities (ARIC) study of middle-aged subjects (age 45 to 64 years), using high-resolution B-mode ultrasound examination of the left common carotid artery, found that 1 standard deviation increase in arterial stiffness was associated with a 15% greater risk of future hypertension, independent of established risk factors and level of BP. In this issue of Hypertension, Dernellis and Panaretou confirmed the findings of Liao et al and extended them to an age range of 35 to 93 years. Aortic stiffness was determined by M-Mode echocardiography by a technique using polynomial regression analysis, calculating aortic systolic and diastolic diameters, and using standard equations to calculate aortic strain, distensibility and stiffness index (β). Progression from normotension to hypertension was related to age and sex, with the incidence rates after 4-year follow-up being lowest in young women (4%) and men (11.5%), and highest in older women (26%) and men (59%).

Using multiple linear regression modeling, they found that aortic stiffness in normotensive individuals was a predictor of future hypertension after correcting for risk factors that included systolic BP, age, sex, body mass index, heart rate, total cholesterol, diabetes, smoking, alcohol consumption, and physical activity; these finding were noted for both young and old subjects and for both sexes.

This report raises questions that deserve attention. First, how is arterial stiffness related to hypertension? Is it a true risk factor or just a risk marker? A true risk factor is suspected of being causative of the disease process. A risk marker is associated with the disease process without being in the causal pathway. Most studies that evaluate arterial stiffness and hypertension have been cross-sectional and thus limit inferences regarding cause and

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effect. The longitudinal study by Dernellis and Panaretou has shown that increased arterial stiffness is antecedent to the development of hypertension, suggesting that the former is a risk factor for the latter. However, recording normal BP with simultaneous echocardiographic measurements is not sufficient to rule out long-standing, transient increases in “hemodynamic load” on blood vessels that could result in previous vascular remodeling, hypertrophy, and increased arterial stiffness. One cannot conclude that isobaric stiffness is present without careful 24-hour ambulatory monitoring of peripheral day/night BP to exclude transient increases in mean arterial pressure and/or PP. Furthermore, demonstrating a temporal relationship is a necessary first step but not necessarily sufficient in establishing causation. Additional proof must be forthcoming. Future studies must test strength of association, consistency, the presence of a dose-response relationship, and a plausible pathogenic pathway between the cause and effect. This will require using a variety of techniques to assess central arterial stiffness, which include PWV, characteristic impedance, and pulse wave analysis.

The Dernellis and Panaretou study is especially noteworthy in demonstrating accelerated arterial stiffness antedating the development of hypertension in young persons. However, their findings would be more convincing if they had studied a more representative young adult age distribution, such as ages 18 to 49 years rather than ages 35 to 64 years.

Second, what potential risk factors have been associated with both increased arterial stiffness and increased BP? An elevated heart rate, as a marker of increase sympathetic and decreased parasympathetic activity, has been shown to precede both the development of arterial stiffness and hypertension. Although controversial, the preponderance of evidence now favors dietary salt-induced arterial stiffness in association with hypertrophy of the arterial wall, alteration of the vascular endothelial cells, and upregulation of angiotensin II receptors, all in the absence of a change in BP. Similarly, there are abundant animal and human studies showing salt-dependent development of arterial stiffness and left ventricular hypertrophy that is independent of an increase in BP. The recent study by Sesso et al. has clearly shown that elevated plasma C-reactive protein was associated with the future development of hypertension in a dose-dependent manner. These findings suggest that hypertension may be an inflammatory disease that is associated with obesity and the metabolic syndrome. This could represent a causative pathway by which inflammation predisposes to both arterial stiffness and hypertension, as well as to cardiovascular and renal disease. In a cross-sectional study of a healthy population, aortic and brachial PWV and PP were associated with increased odds of having an elevated C-reactive protein after adjusting for obesity and metabolic factors. Furthermore, there may be a hormonal pathway acting independently of either metabolic or inflammatory disturbances, with the finding that fasting serum leptin levels were independently associated with arterial distensibility. Adding to a possible inflammation pathway, the HOORN study group showed that increased arterial stiffness developed in patients with impaired glucose tolerance but not progression to frank type 2 diabetes or the onset of hypertension. In addition to environmental factors, there may be a distinct genetic predisposition to the development of premature arterial stiffening and hypertension. Shortened telomere length in white cells, a highly heritable indicator of biologic aging, was associated with wide PP and increased PWV.

To date, no final common pathway has been identified that can explain the association of arterial stiffness with the future development of hypertension. There may be multiple pathways in the mosaic of mechanisms that predispose to hypertension. Much work remains to be performed. However, there is increasing evidence that nitric oxide may play an important role in the regulation of large artery stiffness and ultimately the development of hypertension and atherosclerotic cardiovascular disease. The endothelial-derived substances that regulate vascular tone, cell growth, and blood coagulation in vivo involve the autonomic nervous system, angiotensin and aldosterone receptors, and a cascade of cytokines that ultimately determine the balance between nitric oxide and reactive oxygen species; this balance is important in determining endothelial function, arterial distensibility, and BP levels. From a clinical perspective, the determinants of large artery stiffness and hypertension may represent known risk factors, the residual confounding of unknown risk factors, and the adverse positive feedback effects of vascular changes that affect heart and kidney function.

The findings of Dernellis and Panaretou and of Liao et al., together with earlier studies, provide support for arterial stiffness and hypertension interacting with each other in a bidirectional manner. These studies should stimulate further research as to the interaction of genes, immediate phenotypes, and environmental factors that predispose to accelerated vascular aging and to hypertension. Furthermore, early diagnosis of arterial stiffness with noninvasive techniques before the development of hypertension or cardiovascular complications may identify persons at risk at a time when lifestyle intervention may be useful therapy.

References
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