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EDITORIAL COMMENT

The Aorta and Resistant Hypertension*

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A recent consensus statement from the American Heart Association defined "resistant hypertension" as blood pressure (BP) that remains above goal (<140/90 mm Hg), "in spite of the concurrent use of three antihypertensive agents of different classes. . .where all agents are prescribed at optimal doses" (1). Usually this would involve treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, a calcium-channel blocker, and a diuretic. The prevalence of resistant hypertension is poorly defined worldwide, but surveys in the U.S. (2) suggest that approximately one-quarter of treated patients remain uncontrolled, even when treated by specialists, whom one might assume are appropriately up-titrating treatment. Currently, there are approximately 1 billion people with hypertension worldwide, which suggests that approximately 250 million will have resistant hypertension according to the aforementioned definition and assumptions. This is likely to be an underestimate of the true prevalence because recommended treatment targets are lower (<130/80 mm Hg) in patients most at risk (i.e., those with diabetes, chronic kidney disease), and those with established cardiovascular disease, in whom the definition of resistant hypertension is most likely to apply. Whatever the true figure, resistant hypertension clearly represents a significant burden of disease and prompts consideration of the underlying mechanisms.

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The first question is: "who are these people with resistant hypertension?" The defining feature for most is resistance to systolic pressure control (3). In the Framingham study, of those treated for hypertension, 90% achieved a diastolic goal of <90 mm Hg; less than one-half achieved their systolic pressure goal (4). Similar and remarkably consistent findings have been reported from analyses of the major clinical trials in which diastolic pressure is invariably controlled in the vast majority of patients, but less than one-half achieve their systolic pressure goal (5). Isolated systolic hypertension represents a particular challenge. Older age is the strongest predictor of resistant hypertension. Other potent clinical predictors include the presence of obesity, target organ damage (e.g., left ventricular hypertrophy and chronic kidney disease), smoking, and diabetes (1). Ironically, this list also identifies patients at highest risk of cardiovascular events, in whom control of BP would be particularly beneficial.

The aforementioned characteristics of those most likely to develop resistant hypertension provide important insights into its pathogenesis. The dominant impact of aging suggests that age-related aortic stiffening is likely to be the key factor (6). The potent contribution of renal impairment also suggests that salt and water retention plays an important role, compounded by the reduced capacity of the stiff arterial system to buffer any increase in volume retention.

Arterial stiffening is of paramount importance in the rise in systolic BP with age, the associated decline in diastolic pressure, and the resultant widening of pulse pressure seen with aging (6–8). This aortic aging process is related to structural changes within the media of the vascular wall (9) (Fig. 1). The aorta is designed to smooth the intermittent pulsatile flow of blood emerging from the left ventricle, into smooth flow. The stress of the repetitive strain/relaxation cycle due to the pulsatile nature of the cardiac output is primarily borne by the aortic elastin fibers. Over time, and especially in the presence of hypertension, these elastin fibers become fatigued and fragment, thereby transferring the pulsatile stress to the less compliant collagen fibers within the arterial wall. This process accelerates from middle age, resulting in the development of a less compliant or stiffer aorta (7–10). This stiffening process is further accelerated by: 1) diabetes, through post-translation modification of vascular wall collagen by the deposition of advanced glycation end-products (11,12); and 2) vascular wall calcification (13). Calcification of the aorta and its relationship to enhanced arterial stiffness has been recognized for many years. It is known that degenerate and fragmented elastin fibers are rich in calcium binding sites, and it is conceivable that the exponential rise in the deposition of aortic wall calcium from middle age and its acceleration in the presence of hypertension reflects elastin damage (14). However, enhanced vascular wall calcification has also been noted in smokers, people with diabetes, and those with chronic kidney disease, suggesting a multifactorial process (15). Importantly, the risk factors for the development of resistant hypertension are aligned perfectly with those responsible for the pathogenesis of aortic stiffening. This is unlikely to be a casual association; it is more likely to be a causal relationship. Increased aortic stiffness results in profound disturbances to aortic function and the pulse pressure wave morphology by: 1) increasing the characteristic impedance to flow, perhaps in part explaining the identification of left ventricular hypertrophy as a risk

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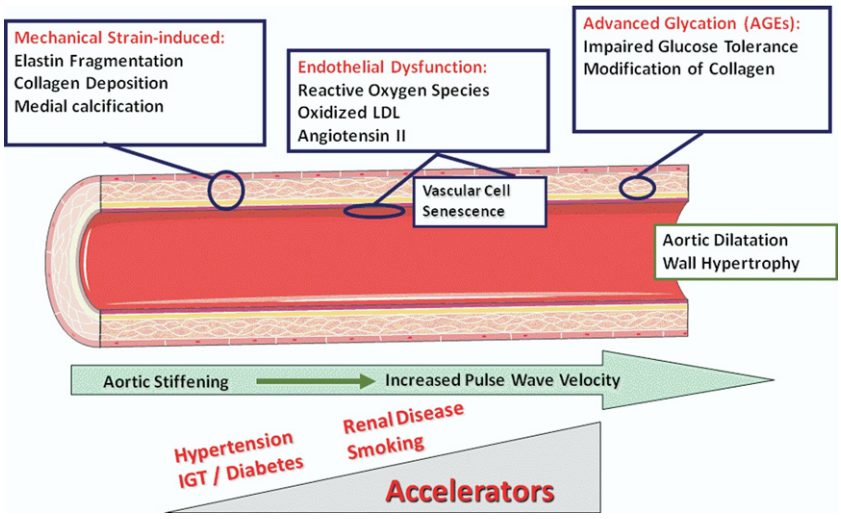

Figure 1 **Factors Influencing the Development of Aortic Stiffness Leading to Resistant Hypertension**

AGE = advanced glycation end-product; IGT = impaired glucose tolerance; LDL = low-density lipoprotein.

factor for resistant hypertension; 2) by increasing pulse wave velocity (PWV) and reducing the time to wave reflection, thereby increasing the likelihood of central aortic systolic pressure augmentation; and 3) by increasing central aortic systolic pressure and pulse pressure and an associated rise in the same brachial pressure parameters with aging—changes that will further accentuate aortic stiffness. The increase in aortic stiffness and reduced aortic capacitance will also render the patient more volume sensitive, compounded by the age-related decline in glomerular filtration rate (16). Moreover, increased stiffness in the aortic arch and carotid artery will reduce baroreceptor responsiveness (16), facilitating the rise in systolic pressure and bedevilling attempts to reduce it.

Although the aforementioned evidence is comprehensive and compelling and strongly implicates aortic stiffness in the pathogenesis of resistant hypertension, it does not provide the "smoking gun." To convince the clinical jury beyond reasonable doubt requires at least 2 further sources of evidence: 1) that aortic stiffness defines the people with resistant hypertension; and 2) that reversal of aortic stiffness, if it could be achieved, would convert a patient from resistant to responsive with regard to BP-lowering treatment. In this issue of the *Journal*, Protogerou et al. (17) provide intriguing evidence to support the first strand of additional evidential support for the aortic stiffness hypothesis, that is, that aortic stiffness defines treatment resistance. They report a post-hoc analysis of data from the REASON (Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind) study, a randomized clinical trial that prospectively evaluated the effects of 12 months of treatment with atenolol versus a low-dose combination therapy of perindopril/indapamide on BP control and arterial hemodynamics in 375 patients (17). Carotid-femoral PWV, a well characterized surrogate for aortic stiffness, was measured at baseline. Patients were then stratified into tertiles of PWV, and their response to BP-lowering therapy over the next 12 months was related to their baseline PWV. There was no impact of baseline PWV on the diastolic BP response to treatment at 12 months; however, the baseline PWV predicted the systolic BP response to treatment. Those with the highest baseline PWV and, thus, aortic stiffness, had the least effective systolic BP control, even despite treatment with more add-on therapy. Moreover, the predictive value of PWV on the systolic BP response was independent of age, sex, mean BP, and cardiovascular risk factors. These important findings suggest that aortic stiffness is a strong independent predictor of the likelihood of resistant hypertension and puts the aorta and its age-related degeneration at the center of the pathogenesis of resistant hypertension.

These findings also raise important philosophical questions about the current treatment strategies for hypertension. The aorta is the forgotten victim of hypertension. Aortic damage due to hypertension is insidious, progressive, and unrelenting. It also sets up a vicious cycle in which subtle early damage serves to accelerate the rise in systolic pressure, which, in turn, causes further degeneration of aortic function. This sets the stage for the mid-life rise in systolic pressure, progressing to isolated systolic hypertension and resistant systolic hypertension. One approach to treatment would be to develop novel therapeutics designed to reverse some of the pathological changes in the aorta and restore responsiveness to BP-lowering treatments. In this regard, pilot studies with collagen crosslink breakers were initially very promising (18), but subsequent results have been somewhat disappointing, with no major impact on brachial systolic pressure in humans. This does not preclude

the possibility that the crosslink breakers may have produced important reductions in central aortic systolic pressure, which was not studied. This is important because the brachial BP response to treatment does not always faithfully reflect the impact of drugs on central aortic pressures (19). There is, however, a simpler approach. Why not identify younger people with mild hypertension and disproportionate stiffening of their aortas for their age, and treat them early with BP-lowering therapy? The rationale is that pressure-mediated mechanical stress is the key factor resulting in elastin fragmentation and aortic stiffening. Thus, treating the cause and preventing progression of early aortic damage should prevent the relentless rise in systolic pressure and ultimately, the costly and often ineffective multidrug treatment of resistant hypertension. Put simply, 1 drug or 4! Nobody is born with resistant hypertension, and preventing its development by limiting aortic damage is likely to be more effective than treating it once aortic damage is established.

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