Arterial Stiffness and Incidence of Systolic Hypertension: The End to the "Chicken-Egg" Question?

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From the early works of the father of biomechanics (Giovanni Alfonso Borelli, 1608–1679) on arterial elasticity[1] to the first quantitative study of vascular elasticity by Charles Smart Roy, 1854–1897)[2] and the later invention of the sphygmomanometer by Scipione Riva-Rocci, 1896–1937), arterial stiffening was considered to reflect aging and to be associated with blood pressure (BP) level.[1] During the past 50 years, thanks to the development of easy-to-use and reasonably reproducible noninvasive methods to measure arterial stiffness,[3] the extensive clinical investigation of human arterial elastic properties led to major advancements in the understanding of cardiovascular disease (CVD) and particularly the pathophysiology of arterial hypertension.[4,5] The work of several research groups, particularly that of the Paris group led by Professor Michel Émile Safar,[6] on the pathophysiology of arterial aging, firmly established the association between increased arterial stiffness and elevated pulse pressure in the elderly.

Throughout the history of "arterial elasticity," the concept of a reciprocal causal association between elevated BP and arterial stiffening is so far prevailing. However, in light of new evidence form large longitudinal prospective studies,[7] including the present study by Zheng and colleagues[8] published in this issue of *The Journal of Clinical Hypertension*, this dogma must now be partly reevaluated and also further developed.

The pathogenesis of essential arterial hypertension is multifactorial, including genetic and environmental factors, renal and neurohumoral factors, as well as deviations from normalcy in vascular structure and hemodynamics.[9] The latter structural vascular abnormalities in the microcirculation and/or macrocirculation lead to increased total peripheral resistance and arterial stiffening, respectively.[9] The specific contribution of each one of these factors in the pathogenesis of hypertension can only be roughly delineated, because of the complexity and interrelation of these mechanisms. However, cumulating evidence shows that vascular abnormalities play an equally important role in the pathogenesis of essential hypertension, as renal vascular volume control, which is the fundamental concept of the Guytonian theory.[9] Studies have shown that alterations in the microcirculation, manifested as capillary rarefaction, take place very early in the pathophysiology of arterial hypertension.[10] Several studies[7,11–15] have also clearly shown that increased arterial stiffness is an independent predictor of the incidence of arterial hypertension, regardless of the method used for its measurement (arterial tonometry,[7] carotid[11] or aortic[12] ultrasound, Doppler method[13]) or the arterial bed (proximal aorta,[12] thoracic-abdominal aorta,[7,13] peripheral arteries[11,14,15]).

In this issue of the *Journal*, Zheng and colleagues[8] showed that in a community-based, prospective, long-term (average time 27 months) follow-up observation study including 2153 individuals with no medical history of arterial hypertension, ankle-brachial pulse wave velocity (PWV) may predict the onset of arterial hypertension, independently of baseline BP level, age, sex, and other major (metabolic or lifestyle-related) confounders, including use of BP-lowering drugs at follow-up visit. Moreover, this prospective study showed for the first time[16] that the incidence of specific hypertension phenotypes, ie, of isolated systolic hypertension, but not of isolated diastolic hypertension, is related to increased arterial stiffness. This is clear evidence that isolated diastolic hypertension is caused by different vascular mechanisms, ie, either volume overload and/or total peripheral resistance increase.

Arterial stiffening is undoubtedly the hallmark of normal vascular aging that can be potentially reversible and precipitated by several metabolic and inflammatory factors.[4,5] There is also strong evidence supporting the genetic determination of arterial stiffenning.[4,5] However, the second main finding of the study by Zheng and colleagues[8] that baseline BP level is not associated with arterial stiffness measurement at follow-up visit after correcting for baseline stiffness values, puts in question the so-far prevailing theory about the acceleration of arterial stiffening in the presence of chronically elevated BP. This finding is in line with recently published data by Kaess and colleagues[4] and, if further confirmed, might put an end to this "chicken-egg" problem.

These observations have important clinical implications since they highlight even more emphatically the distinct role of arterial stiffness in CVD risk assessment and CVD prevention and management. They also further highlight the known ability of specific classes of BP-lowering drugs to have destiffening effects, acting directly on the arterial wall properties,[17] beyond their acute passive effect on the function of the arteries.

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Finally, they are in line with the hypothesis of Martyn and Greenwald that reduced elastin deposition might be programmed in early life (eg, as in low-birth-weight babies), leading to increased arterial stiffness and thus might predict subsequent elevated pulse pressure and hypertension.[18]

Arterial stiffness measurement has already taken its place in clinical practice. In 2007, the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines included aortic stiffness, assessed by carotid to femoral PWV (cf-PWV), among the parameters for the evaluation of cardiovascular risk; this recommendation was upgraded in recent guidelines[19] (recommendation class IIa, level of evidence B). An increase of 1 m/s in PWV increases the age-, sex-, and CVD risk factor–adjusted risk by 14%, 15%, and 15% for total CVD events, CVD mortality, and all-cause mortality, respectively. Moreover, cf-PWV reclassifies the CVD risk of patients at intermediate risk (ie, of those in particular need for better CVD risk stratification) in a clinically meaningful percentage (13%).[20] Today, reference values and a high-risk cutoff value are well established for cf-PWV, bringing the clinical application of arterial stiffness for the optimization cardiovascular risk assessment in hypertensive patients a major step forward.[19,21] However, several other clinically useful aspects of arterial stiffness remain poorly investigated, such as its ability to predict the BP response to drug treatment (or to guide drug selection)[22] and its ability to detect individuals at risk for developing orthostatic hypotension,[23] and thus guide BP management.

The future perspectives for the clinical application of arterial stiffness appear even more promising. In the recent past years, the assessment of arterial stiffness has become feasible both in static and 24-hour ambulatory conditions, by the use of an operator-independent, validated, automated oscillometric brachial cuff-based device.[24,25] Most importantly, arterial stiffness as assessed by this method predicts the incidence of mortality,[26] providing important data on the physiology and variability of arterial stiffness.[27] For that reason it is highly expected that in the following years the cardinal role of arterial stiffness in the pathogenesis, as clearly depicted in the study of Zheng and colleagues, as well as in the prevention and management of arterial hypertension, will be further revealed and potentially modify the clinical practice guidelines.

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