Arterial Stiffness in Hypertension and Function of Large Arteries

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BACKGROUND
Arterial stiffness—typically assessed from non-invasive measurement of pulse wave velocity along a straight portion of the vascular tree between the right common carotid and femoral arteries—is a reliable predictor of cardiovascular risk in patients with essential hypertension.

METHODS
We reviewed how carotid-femoral pulse wave velocity increases with age and is significantly higher in hypertension (than in age- and gender-matched individuals without hypertension), particularly when hypertension is associated with diabetes mellitus.

RESULTS
From the elastic aorta to the muscular peripheral arteries of young healthy individuals, there is a gradual but significant increase in stiffness, with a specific gradient. This moderates the transmission of pulsatile pressure towards the periphery, thus protecting the microcirculatory network. The heterogeneity of stiffness between the elastic and muscular arteries causes the gradient to disappear or be inversed with aging, particularly in long-standing hypertension.

CONCLUSIONS
In hypertension therefore, pulsatile pressure transmission to the microcirculation is augmented, increasing the potential risk of damage to the brain, the heart, and the kidney. Furthermore, elevated pulse pressure exacerbates end-stage renal disease, particularly in older hypertensive individuals. With increasing age, the elastin content of vessel walls declines throughout the arterial network, and arterial stiffening increases further due to the presence of rigid wall material such as collagen, but also fibronectin, proteoglycans, and vascular calcification. Certain genes, mainly related to angiotensin and/or aldosterone, affect this aging process and contribute to the extent of arterial stiffness, which can independently affect both forward and reflected pressure waves.

Keywords: arterial stiffness; blood pressure; hypertension

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In individuals with either normal blood pressure (BP) or hypertension, BP levels vary considerably according to changes in two parameters: the source of flow, i.e., the left ventricle of the heart, where output is pulsatile, and the peripheral tissues, i.e., arteries, where flow is practically continuous. The interactions between steady and pulsatile flow within the heart, the arterial tree and the peripheral organs are typically assessed by measuring BP with a cuff located in a convenient—though in pathophysiological terms somewhat inappropriate—arterial site, i.e., the brachial artery.

However, in a longitudinal study of 71,629 individuals, Protogerou *et al.* showed that cardiac output and capillary pressure—two major hemodynamic characteristics of hypertension—do not vary notably between individuals with and those without hypertension.[1–8] Cardiac output levels are typically within the normal range, and capillary pressure remains similar irrespective of the presence of hypertension, i.e., both in normal physiological conditions and subsequent to arteriolar changes. It is noteworthy that all study participants had similar sodium excretion levels, i.e., more or less normal renal function.

One consistent hallmark of capillary circulation is the absence of notable variations in capillary pressure, regardless of BP levels.[2] When BP is elevated, the myogenic tone of precapillary arterioles induces vasoconstriction, which limits transmission of this high pressure to the capillary bed. Given that the resistance of precapillary arterioles and the level of capillary pressure are not significantly modified, the vascular bed is thus protected from damage that high BP can potentially cause. Panel a of Figure 1 illustrates the changes in BP that occur between the larger arteries (pulsatile flow) and the capillary bed (steady flow) to ensure a low capillary pressure. Classically, the changes in vascular resistance observed between the conduit arteries and the microcirculation occur very abruptly over the short distance between the arteries and veins (Figure 1, Panel a). High vascular resistance is therefore associated with a reduction in both pulsatile phenomena and steady flow, resulting in a quasitotal steady flow through resistance vessels. Panel b of Figure 1 shows the possible hemodynamic changes that can be observed in both normotension

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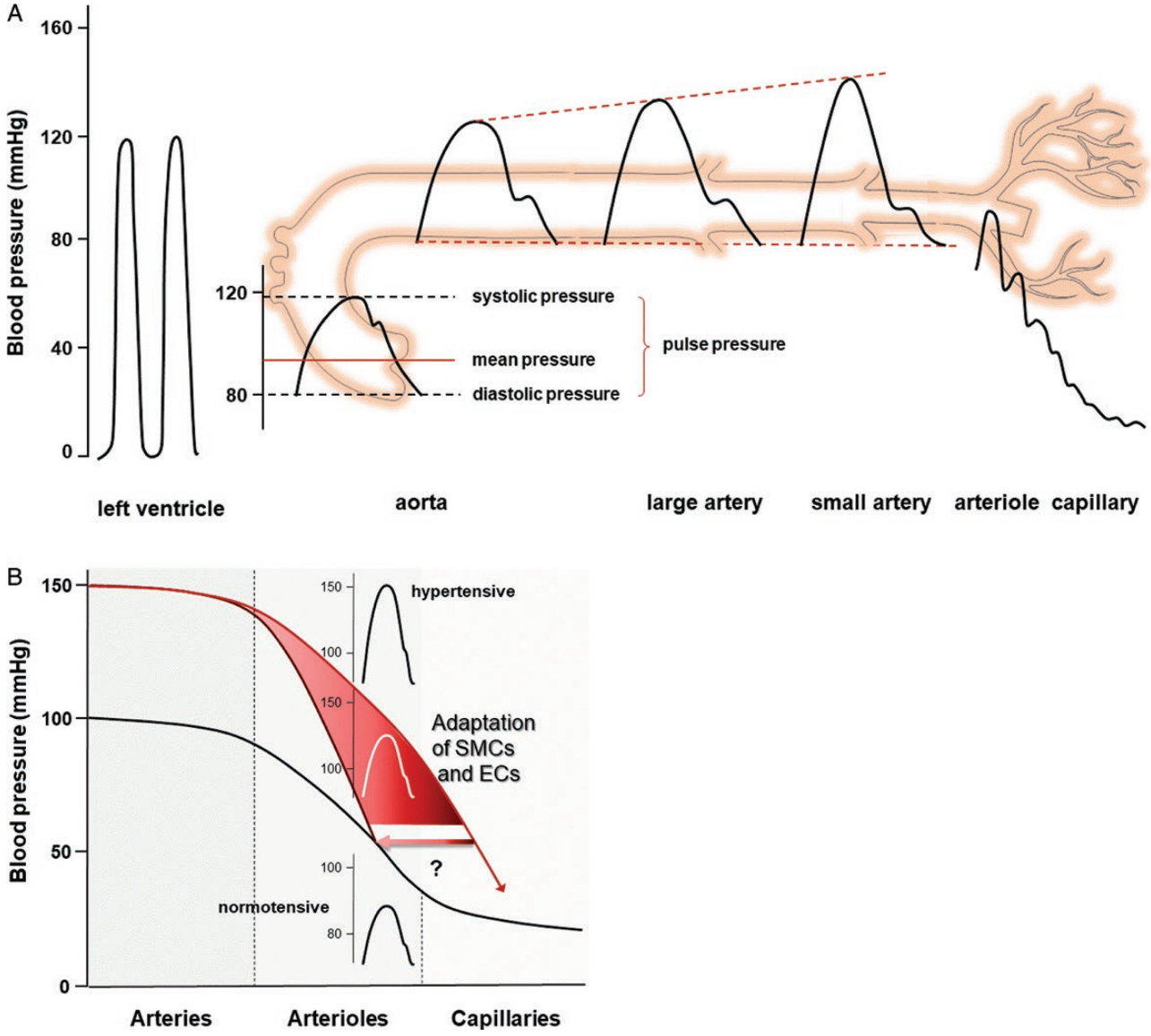

Figure 1. Principal aspects of the transition from pulsatile to steady blood pressure (BP) along the arterial tree. Panel **a** shows the usual modifications in BP along the arterial tree. Panel **b** shows the BP changes depending on endothelium, smooth muscle (SMCs), and extra-cellular (ECs) cells, which may be associated with possible hypertensive modifications. Reproduced with permission from Safar *et al.*[5]

and hypertension. The upper and lower curves of Panel b characterize these two situations that lead to the same low capillary pressure level. Thus, in order to avoid increased capillary pressure in hypertension, adaptive changes in the mechanosensitive vasomotor function of the vascular endothelium and smooth muscle are necessary, possibly including the presence of a steeper slope of the pressure–arterial diameter relationship, as shown by the middle curve of Panel b.[3–5]

We propose a clinical overview of the possible mechanisms behind the transition between normotensive and hypertensive states, with a specific focus first, on the clinical features of aortic stiffness and its propagation along the hypertensive tree, and second, the clinical and biological correlations between aortic stiffness and the possible modifications in renal, cardiac, and cerebral structure and function in individuals with hypertension.[6–8] In this setting, the respective roles of forward and backward reflected pressure waves will be discussed.

ARTERIAL STIFFNESS IN HYPERTENSIVE SUBJECTS: FROM NON-PROPAGATING TO PROPAGATING MODELS OF CIRCULATION

BP measurements: from the Windkessel model to pulse wave velocity (PWV)

The Windkessel model illustrates how the large (elastic) compartment of the arterial bed instantly adjusts to the periodically ejected left ventricular blood stroke volume—which is partly stored during systole and then drained during diastole—enabling adequate cardiac output and thus continuous

perfusion of peripheral organs and tissues. It is a non-propagative representation of the cardiovascular system that relies on cardiac stretching but also on two distinct aortic properties: distension and relaxation. However, the Moens–Korteweg equation—$PWV^2 = Eh/2R\rho$, where E is Young's elastic modulus of the wall, h the wall thickness, R the internal vessel radius, and ρ the blood density—provides a more accurate representation of the cardiovascular system since it also includes propagation and velocity.[9] This model shows how pulse pressure (PP) waves travel faster in stiffer arteries and therefore confirms PWV as a more reliable index of hypertensive aortic stiffness.[10]

BP measurement

Given that studies have confirmed the effect of hemodynamic parameters on PWV, this equation provides a clearer demonstration of the role played by the arterial elastic modulus, increased aortic stiffness, elasticity, and pulsatility in hypertension, particularly when the ratio of wall thickness to arterial diameter, and the blood density are taken into consideration. Importantly, aortic stiffness and elevated pulsatility are mostly observed in individuals with systolic hypertension and/or in hypertensive individuals with a disproportionate increase in systolic blood pressure compared with diastolic blood pressure. PWV—the speed at which the aortic wave travels, in cm/s—is usually measured in longitudinal arterial sections, mainly between the carotid and femoral vessels, illustrating the clinical relevance of this section of the vascular tree (Figure 2).[5,11] In age-, gender-, and body mass index-matched non-diabetic individuals, aortic PWV is significantly higher in hypertensive than normotensive populations. This finding is also particularly notable in patients with concomitant hypertension and diabetes mellitus, even in the presence of elevated HbA1c alone.[12,13] Furthermore, PWV increases significantly and linearly with age.[14] Elevated PWV and an increased aortic diameter are standard features of hypertension and together form the most reliable independent predictor of cardiovascular risk in the elderly population.[15]

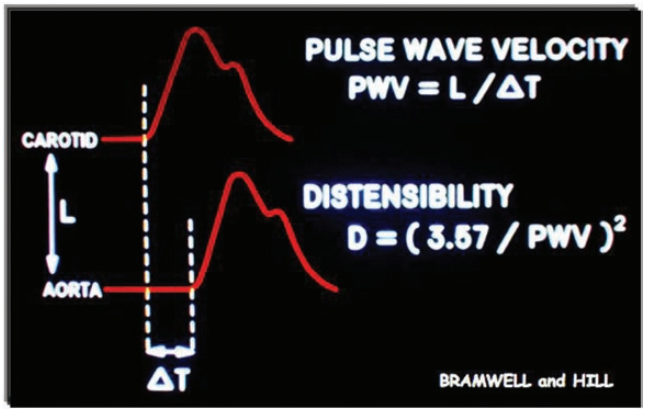

Figure 2. Pulse wave velocity (PWV) and distensibility (*D*) as a function of the distance between the carotid and aortic sites (*L*) and the delta *T*, the time interval between the two pressure waves as calculated from the Bramwell and Hill formula. Reproduced with permission from Safar *et al.*[5]

PWV and the aging process

Between the aorta and the peripheral arteries, PWV becomes increasingly greater. This progressive stiffness gradient between the central and peripheral arteries[16] generates backward traveling (i.e., away from the microcirculation) pressure waves that dampen the amount of energy that is propagated into the microcirculation. This reduction in distal pressure transmission protects the microcirculation. If however the stiffness gradient disappears or is reversed, PP is insufficiently dampened and the excess pressure is directly transmitted to the small peripheral arteries and the microcirculation, with a significant impact on cardiovascular risk, mostly through vessel damage.[17] Although this is exacerbated with advancing age, it is noteworthy that antihypertensive drug therapy can still be effective.

With advancing age, arterial stiffening is more prevalent in the aorta (measured by aortic PWV) than in peripheral arteries (measured by brachial PWV).[18] Zhang *et al.* reported this trend, and also the discrepancy in aging between elastic and muscular arteries in both men and women.[19] The now well-established phenomenon of age-related arterial stiffening leads to a reduction in the stiffness gradient between the aorta and the peripheral arteries, and likely exacerbates the deleterious effect of pulsatile energy on the microcirculation. In 305 patients with end-stage renal disease, Pannier *et al.* were the first to investigate PWV in elastic arteries and its prognostic value in terms of cardiovascular mortality.[20] More recently, Fortier *et al.* showed that in a population of patients on dialysis, a biomarker calculated from the ratio between aortic and brachial PWV was also significantly associated with mortality.[21] Unlike PWV, this ratio was also shown to be a BP-independent biomarker of vascular aging.[22] Niiranen *et al.* were however unable to demonstrate a major prognostic value for this ratio.[23] Further investigations are therefore required to confirm the prognostic value of the stiffness gradient, particularly in the presence of vessel malformation and/or ethnic particularities.

AORTIC STIFFNESS AND RENAL, CARDIAC, AND CAROTID–CEREBRAL CIRCULATIONS IN THE PRESENCE OF HYPERTENSIVE DAMAGE

This section presents a brief summary of the role of constricting and relaxing factors on arterial stiffness, and subsequently the contribution of the kidney, the heart, and, more briefly, the carotid–cerebral circulation. The contribution of the kidney is explained in the context of both the kidney itself and the heart.

First, in earlier studies on hypertension, changes in large and small artery stiffness were mainly attributed to extracellular matrix proteins, and their influence on the elastin/collagen ratio. The progressive age-related decrease in elastin content was seen to exacerbate the prominent age-related increase in collagen content, and hence the development of arterial stiffness. However, recent reports on animal models of the hypertensive vascular endothelium have further highlighted the role of both vasoconstricting and vasorelaxant factors.[24,25] In hypertension, constricting factors modulate arterial and arteriolar properties through their

equilibrium with nitric oxide bioactivity,[24] and contribute to the mechanism of vascular stiffening. Investigations into cellular and/or molecular determinants of vascular stiffness have expanded this viewpoint to include proteins that regulate vascular smooth muscle cell contractility and cell–extracellular matrix interactions, most of which are linked to focal adhesion molecules.[25] Proinflammatory factors, as confirmed by C-reactive protein levels, may also play a role in this process. These observations show that hypertension-mediated changes and attenuation of the arterial stiffness gradient are mainly attributable to the circulation of blood within the kidney, the heart, and the brain.

Second, the prominent role played by the kidney in the mechanisms of hypertension is also now widely acknowledged, and known to be influenced by mean arterial pressure, cardiac output, vascular resistance, and above all, by renal blood flow.[26] PP and PWV—two major indices of aortic stiffness—have also been shown to be significant predictors not only of cardiovascular risk but also of the age-related decline in glomerular filtration rate (GFR). From a physiological standpoint, precapillary arterioles—known to provide some 75% of the resistance of the vascular bed—protect the capillaries of the heart and the brain from elevated mean and pulsatile BP energy. Within the kidney however, efferent arteriolar resistance is lower than that of afferent arterioles and causes a relatively small pressure reduction throughout afferent glomerular arterioles. PP in the glomeruli is therefore relatively high, approximating 60% of the arterial values. Glomerular filtration is protected by this mechanism, whereas the capillaries are exposed to the potential damaging effect of pulsatile pressure. A combination of myogenic tone in the afferent arteriole and tubuloglomerular feedback is responsible for the autoregulation of renal blood flow.[27] This important process is achieved over a wide range of perfusion pressures, classically defined in terms of "steady pressure." However, increased PP significantly affects renal hemodynamics (and myogenic tone in the afferent arterioles) in animal and human models where PP is disproportionate to mean arterial pressure. This has been observed in the remnant kidney model in animals, and is also found in humans with advancing age (>50 years), thus suggesting a possible mechanism for the age-related decline in GFR. In their study of the renal resistive component of BP, Hashimoto and Ito made notable observations to explain this particularity,[28] including the fact that most of the patients in their study had hypertension and were undergoing hemodialysis for renal failure. The specific components of BP in these patients are known to be elevated systolic blood pressure and normal or even low diastolic blood pressure. Observations such as these are consistently associated with increased stiffness of large conduit arteries and early wave reflections. Although mean arterial pressure itself may affect the stiffening process, the presence of large artery stiffness and calcifications, possibly due to uncontrolled calcium-phosphate homeostasis, has a greater impact. This hemodynamic change affects vascular remodeling, with dilation of elastic and muscular-type arteries, and increased wall thickness. In patients with end-stage renal disease, arterial remodeling and above all, increased arterial stiffness—as measured from PWV—are independent predictors of all-cause mortality and cardiovascular mortality in particular. One therapeutic trial conducted by Guerin *et al.* in end-stage renal disease patients showed that following long-term BP reduction, cardiovascular survival rates were mainly improved in patients with adequate control of both BP and PWV.[29] Patients with adequate BP reduction but with elevated PWV did not survive. This is a clear demonstration of the deleterious impact of increased aortic stiffness on morbid renal and arterial events.

Third, similar findings have been reported for the heart in atherosclerotic patients undergoing coronary angiography.[30] Between the ascending and terminal aorta, PP amplification is consistently 10 mm Hg higher at the renal site ($P < 0.001$), whereas mean arterial pressure remains unchanged in the same vascular territory. This aspect of PP amplification is significantly associated with the presence of proteinuria. Furthermore, increases in plasma creatinine and aortic stiffness are independently and positively correlated ($P < 0.001$) in these patients. This has been observed in both cross-sectional and longitudinal studies. In addition, most observations linking PP, arterial stiffness, and renal function are made in patients ≥60 years of age and/or in the presence of renal grafts. Arterial stiffness and post-transplant GFR decline in renal transplant patients and their donors have also been studied both 1 and 9 years post-transplantation.[31] During the first year, the decline in GFR was related to smoking and acute graft rejection, whereas in the later phase, it was significantly and exclusively related to donor age and once again, the degree of aortic stiffness.

The variability in symptoms and the clinical characteristics—particularly in terms of arterial stiffness and kidney changes—of individuals with hypertension, mean there can be no simple approach to improving the prognosis of ischemic coronary heart disease in typical clinical practice. However, recent work in the field of artificial intelligence, and notably based on decision tree models and artificial neural networks,[32–35] has opened up the way to predictive medicine based on effective algorithm models to predict ischemic coronary heart disease. These studies are now focusing on the use of PWV measurements and the calculation of an individual PWV index to predict the onset of coronary heart disease, with the use of additional non-linear models to ensure particularly high levels of accuracy.[32–35]

Fourth, in hypertensive humans with severe coronary and/or renal damage, the correlations with PP and GFR show that both parameters are substantially mediated by arterial stiffness, and not exclusively by mean arterial pressure or vascular resistance, and therefore play an important role in cardiovascular risk. Similar observations have also been reported with regard to the brain and hemodynamic parameters of the carotid and/or cerebral arteries.[36,37] It is hoped that the gaps in our current understanding of the extent of the impact of hypertension on the brain will be filled by more extensive investigations in the future, and in particular, that they will throw more light on the mechanisms of vascular dementia, Alzheimer's disease, and cognitive decline.

CONCLUSIONS AND FUTURE PERSPECTIVES

Seminal studies on the pathophysiology of essential hypertension have constantly focused on peripheral vessels—mainly small arteries and larger arterioles—where the

diameter of the lumen is reduced, the medial wall significantly thickened, and the media-to-lumen ratio substantially increased.[38] In this review, we have summarized data showing that hypertension affects not only small arteries and arterioles of peripheral vessels but also larger arteries. Aortic stiffening is a frequently observed feature. Furthermore, between the aorta and the peripheral arteries, there is a progressive and significant increase in PWV. Predominant aortic rather than peripheral artery stiffening modulates pressure wave transmission thus increasing the risk of damage to the microcirculation.

Large arteries therefore have three important properties. First, they play a role in the mechanism of cardiac, cerebral, and renal changes in hypertension, the latter corresponding to Guyton's classic concepts. Second, both vascular endothelial and smooth muscle cells undergo changes including vasoconstriction and vasodilation, age-related reductions in elastin properties, and, most importantly, the development of rigid arterial-wall material, including not only collagen, but also fibronectin, proteoglycans, and arterial calcification.[25] Lastly, drug therapies exert significant effects on arterial-wall properties, not only through changes in BP levels but also via their effects on the composition of the vascular wall. Genotypic interactions are thus prominent considerations.[39]

Ong *et al.* have shown that antihypertensive therapy may counteract arterial stiffness beyond any effect on BP and possibly through mechanisms implying sustained unloading of the arterial wall.[40] In this context, the role of genotypic interactions has been suggested, such as that observed with the sacubitril–valsartan combination[41] or with combined angiotensin receptor modulations.[42] It is also noteworthy that BP is constantly affected by both forward-traveling and reflected (backward-traveling) pressure waves, which act independently—though with distinct levels of impact—and merit further investigation in terms of their outcome during long-term treatment of hypertension.[43]

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DISCLOSURE

The authors declared no conflict of interest.

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