Recent Advances in Arterial Stiffness and Wave Reflection in Human Hypertension

Stéphane Laurent, Pierre Boutouyrie

In recent years, great emphasis has been placed on the role of arterial stiffness and wave reflection in the development of cardiovascular (CV) diseases. Arterial stiffness and wave reflections, which are now well accepted as the most important determinants of increasing systolic and pulse pressures in aging societies, are increasingly used in the clinical assessment of patients with hypertension and various CV risk factors. This review addresses recent advances in our understanding of the role played by arterial stiffness and wave reflection in the pathophysiology and treatment of human hypertension. According to the editorial rules for "Hypertension Highlights", and to better focus on recent research, apart from large clinical trials, only articles published during the last 2 years are quoted in this review.

Determinants Of Arterial Stiffness: Role of Smooth Muscle Cells and Inflammation

Research on the molecular determinants of arterial stiffness has focused for years on the structure and amount of the main load bearing proteins: elastin and collagens. Indeed, aging and blood pressure, the two major determinants of arterial stiffness, are associated with a number of molecular changes of the load-bearing media of elastic arteries: the orderly arrangement of elastic fibers and laminae is gradually lost over time, and thinning, splitting, fraying, and fragmentation are observed. The degeneration of elastic fibers is associated with an increase in collagenous material and in ground substance, often accompanied by calcium deposition in ground substance and in degenerate elastic fibers.

However, quantitative changes in elastin and collagen may not explain, by themselves, paradoxical observations. For instance, the changes in arterial wall material which accompany arterial hypertrophy in animal models of essential hypertension (SHRs and SHR-SPs) and in middle-age hypertensive patients are not necessarily associated with an increased isobaric stiffness. We suggested that adaptive mechanisms may include a rearrangement of the arterial wall material through cell–matrix connections, with a major role of integrins. This remodeling may involve qualitative and quantitative changes in arterial wall components leading to redistribution of mechanical load toward elastic materials.

In this respect, the dedifferentiation of smooth muscle cells (SMCs), leading to arterial wall hypertrophy, and the number of elastin/SMC connections, which influences the extent of elastin network anchorage to SMCs, may play an important role.

The role of contractile proteins of SMCs was illustrated by the discovery of an increased aortic stiffness in a genetic disease combining thoracic aortic aneurysm and/or aortic dissection and patent ductus arteriosus. In patients with MYH11 mutation, altering the C-terminal coiled-coil region of the smooth muscle myosin heavy chain, an increased aortic stiffness was observed, in parallel with medial degeneration and very low SMC content of the aorta. This is the first example that direct changes in a contractile protein produced specifically in SMC may alter arterial stiffness.

Recent studies underlined the role of inflammation in the stiffening of large arteries. The inflammation process, either acute during Salmonella typhi vaccination, or chronic during rheumatoid arthritis or systemic lupus erythematosus, has been reported to stiffen the large arteries. This may occur through various mechanisms including endothelial dysfunction, cell release of a number of inducible matrix metalloproteinases (including matrix metalloproteinase [MMP]-9), medial calcifications, changes in proteoglycan composition and state of hydration, and cellular infiltration around the vasa vasorum leading to vessel ischemia.

Whether arterial stiffening was associated with inflammation in essential hypertension was only recently demonstrated through the relationships between arterial stiffness and either tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), or high sensitive C-reactive protein (hs-CRP). The primary proinflammatory cytokines TNF-α and IL-6 are the main inducers for the hepatic synthesis of hs-CRP. Hs-CRP and IL-6 are independent predictors of increased risk of coronary artery disease. IL-6 and TNF-α are also independent risk factors for high BP in apparently healthy subjects. In untreated patients with essential hypertension, arterial stiffness, assessed through carotid-femoral pulse wave velocity, was significantly related with hs-CRP and IL-6. Baseline hs-CRP was not only an independent predictor of carotid-femoral pulse wave velocity and central augmentation in-
but also of the reduction in peripheral pulse pressure after antihypertensive treatment during the REASON study.12

**Arterial Stiffening, Pulse Pressure, and Microvascular Damage**

Our understanding of the pathophysiology of arterial stiffness and wave reflection in hypertension has gained from studies showing the respective roles of aortic diameter and stiffness in the generation of central PP and the damage of microvessels by pulse pressure.

Indeed, data from the Framingham study suggest that reduced aortic diameter may play an important role in the genesis of increased functional stiffness of the aorta. Mitchell et al13 demonstrated, in older subjects with uncomplicated systolic hypertension, that aortic stiffness, determined by carotid-femoral PWV, was not significantly higher in hypertensives than in normotensives after adjustment to MBP, whereas increased characteristic impedance, calculated from the ratio of change in carotid pressure and aortic flow in early systole, remained highly significant.13 Increased characteristic impedance in hypertensive men was attributable to decreased aortic effective diameter, with no difference in aortic stiffness at comparable MBP. These findings are not consistent with the hypothesis of secondary aortic degeneration, dilation, and wall stiffening. They rather suggest that reduced aortic diameter could be an initiating mechanism of systolic hypertension, leading to an impedance mismatch between ventricular ejection and large artery properties. However, aortic diameter was not directly measured in this work,13 and these results should be confirmed by further studies.

Although the role played by large artery stiffness in the generation of systolic hypertension is well accepted, the role of small artery stiffness has been less studied, particularly in humans. This is likely because of the difficulty in obtaining gluteal subcutaneous tissue from patients. The inward remodeling of resistance vessels in hypertensive patients is associated with an increased wall stiffness.14 Wall stiffness is a limiting factor of wall strain for a given loading blood pressure. Thus, any increase in wall stiffness tends to reduce the lumen diameter for a given smooth muscle tone and blood pressure, leading to increased wave reflections and central PP, which in turn may represent a trigger for hypertrophic remodeling of small arteries. However, arterial stiffness of resistive arteries did not correlate with systolic blood pressure, media/lumen ratio, or left ventricular mass index, in hypertensive and normotensive subjects.15 This important area remains to be further investigated.

The damaging effect of local pulse pressure has been well demonstrated on large arteries, but to a lesser extent on small arteries. Elevated PP may stimulate hypertrophy, remodeling, or rarefaction in the microcirculation, leading to increased resistance to mean flow. An illustration of such pathogenic mechanism may be given by the demonstration, in the Framingham Heart Study offspring cohort, that aortic stiffness and increased pressure pulsatility were closely related with blunted microvascular reactivity to ischemic stress, in multivariable models that adjusted for cardiovascular disease risk factors.16 However, alternative explanations include: (1) a common pathogenesis, which may explain the damage of both large and small arteries; (2) an inward remodeling and altered vasodilatation of small arteries, which may enhance wave reflections and central pulse pressure.

Recent studies showed a close relationship between microvascular damage in brain and kidney and either pulse pressure or arterial stiffness. Indeed, significant and independent relationships have been demonstrated between carotid stiffness and glomerular filtration rate (GFR) in patients with mild to moderate chronic kidney disease,17 between brachial pulse pressure and GFR in elderly patients with never-treated isolated systolic hypertension,18 and between arterial stiffness and cognitive impairment in elderly subjects attending a geriatric outpatient clinic.19

However, the mechanism of such association has not yet been firmly established. O'Rourke and Safar20 recently suggested a pathophysiological explanation on the basis of differential input impedance in the brain and kidney compared with other systemic vascular beds. The unique features of the kidney and brain are that they are continually and passively perfused at high-volume flow throughout systole and diastole. Their vascular resistance is very low, so that in comparison to other vascular beds resistance is closer to input and characteristic impedance. Torrential flow and low resistance to flow in these organs exposes small arterial vessels to the high-pressure fluctuations that exist in the carotid, vertebral, and renal arteries. Such fluctuations, measurable as central pulse pressure, increase 3- to 4-fold with age. Exposure of small vessels to highly pulsatile pressure and flow may explain microvascular damage and resulting renal insufficiency and intellectual deterioration.21
PWV measured outside the aortic track, at the upper (brachial PWV) or lower limb (femoro-tibial PWV), was unable to predict cardiovascular outcome in ESRD patients. Although carotid-femoral PWV and carotid stiffness provide similar information on the impact of aging on large artery stiffness in normal subjects, this is not the case for hypertension or diabetes. In these cases, the aorta stiffened more than the carotid artery with age and other CV risk factors. Thus, aortic stiffness and carotid stiffness cannot be used as interchangeable predictors in high-risk patients. Novel echotracking apparatus, analyzing arterial stiffness not only in the circumferential direction but also in the longitudinal axis, may help to understand the relationships between carotid plaque and stiffness.

Central augmentation index (AIx) and pulse pressure, directly measured by carotid tonometry, have been shown to be independent predictors of all-cause mortality in ESRD patients. These findings have been recently extended to the hypertensive patients of the CAFE study, and to patients undergoing percutaneous coronary intervention, in whom central PP and augmentation index, estimated using a transfer function from radial artery tonometry, were predictive of CV events. However, data concerning the predictive values of both these parameters in the general population are scarce. In older female hypertensive patients, data from the ANBP2 study showed no benefit in use of carotid applanation tonometry (augmentation index or total arterial compliance) over brachial cuff pressure in prognosis. Although analytic methods in this study have been questioned, the lack of additive predictive value may be explained by the lack of amplification of PP between brachial and central PP at this age. Thus, the additive predictive value of central PP and AIx may rather concern younger subjects. In this respect, the Anglo-Cardiff study showed, in healthy normotensive individuals, that the age-related changes in AIx and aortic PWV were nonlinear, with AIx increasing more in younger individuals, whereas the changes in PWV were more prominent in older individuals. These data suggest that AIx might be a more sensitive marker of arterial stiffening and risk in younger individuals but aortic PWV was likely to be a better measure in older individuals.

Therapeutics of Arterial Stiffness

A large number of publications and several reviews reported the changes in arterial stiffness and wave reflections after various interventions, either nonpharmacological or pharmacological. Non pharmacological treatments which are able to reduce arterial stiffness include exercise training, dietary changes (including weight loss, low salt diet, moderate alcohol consumption, garlic powder, ω-linoleic acid, dark chocolate, and fish oil), and hormone replacement therapy. Pharmacological treatments which are able to reduce arterial stiffness include (1) antihypertensive treatment, such as diuretics, β-blockers, ACE inhibitors, AT1 blockers, and calcium channel antagonists; (2) treatments of congestive heart failure, such as ACE inhibitors, nitrates, and aldosterone antagonists; (3) hypolipidemic agents such as statins; (4) antidiabetic agents, such as thiazolidinediones; and (5) advance-glycation end products (AGE)-breakers.

Whether the reduction in arterial stiffness after antihypertensive treatment is only attributable to BP lowering, or additional BP-independent effects are involved, is still debated. We recently showed a direct BP-independent effect of ACE inhibitors on arterial stiffness. We used an experimental design in which hypertensive patients with type 2 diabetes, responding to 1 month treatment with 4 mg perindopril, were randomized double-blind to either 4 mg perindopril or 8 mg perindopril for 6 months. After 7 months treatment, although the reduction in 24 hour ambulatory blood pressure was not significantly different between 4 mg and 8 mg perindopril, carotid distensibility increased more after 8 mg perindopril compared with 4 mg perindopril. Thus, to our knowledge, this is the first time that a reduction in arterial stiffness has been unequivocally shown to occur in response to long-term ACEI inhibition independent of chronic BP reduction. These results also suggest that long term administration of high doses (8 mg) of perindopril is required to improve carotid structure and function in hypertensive patients with type 2 diabetes once BP is controlled. These data are consistent with the results of large clinical trials, such as HOPE and EUROPA, which used higher doses of ACE inhibitors in patients with a high CV risk, including patients with hypertension and type 2 diabetes.

Perspectives: Reduction in Arterial Stiffness and Outcome Protection

Although measures of stiffness and wave reflection provide useful prognostic information concerning the occurrence of CV events in various populations, the predictive value of arterial stiffness and wave reflection attenuation for the reduction in CV events under treatment is yet to be demonstrated. Many years elapsed between the demonstration that left ventricular hypertrophy (LVH) and albuminuria had predictive value for CV events, and the results of the LIFE and RENAAL trials, which showed that the regression of LVH and albuminuria, respectively, were predictive of the reduction in CV events, independently of the normalization of usual CV risk factors. Although LVH and albuminuria are well accepted as intermediate end points, they reflect an advanced damage of target organs, and markers of earlier damage are required, such as abnormal arterial stiffness and wave reflection.

Thus, a major issue would be to determine whether a reduction in PWV or wave reflection is associated with a concomitant reduction in CV events, independently of the normalization of classical CV risk factors. This is likely because arterial stiffness decrease reflects the true reduction of arterial wall damage, whereas the reduction in BP, glycemia, and lipids may not. Indeed, BP, glycemia, and lipids can be normalized in a few weeks by using antihypertensive, antidiabetic, and lipid-lowering drugs, leading to a strong reduction in CV risk scores, but without yet any improvement of atherosclerotic lesions and arterial stiffness, which may require a long-lasting correction of biochemical abnormalities. A temporal dissociation is thus expected between the improvement of CV risk factors and a still high arterial stiffness. Measurement of arterial stiffness and wave reflection may avoid patients being mistakenly classified as at low
or moderate risk, when they actually have an abnormally high arterial stiffness or central PP placing them within a higher risk group.

A direct answer to the issue of the predictive value of aortic stiffness attenuation for the reduction of CV events has been given in ESRD patients but not in other populations, particularly those at lower but still high CV risk, ie, with hypertension, dyslipidemia, diabetes, or moderate CKD. Similarly, whether the reduction in central PP is associated with a concomitant reduction in CV events, independently of the normalization of classical CV risk factors, remains to be demonstrated. There are indirect arguments. In the LIFE and ASCOT studies, losartan- and amlodipine-based treatments, respectively, proved to be more effective than atenolol-based treatments for reducing CV events. β-blockers devoid of vasodilating properties are less effective for reducing central PP and Aix than vasodilating β-blockers (including celiprolol, dilevalol, and nebivolol), and other antihypertensive drugs. Indeed, nonvasodilating β-blockers may unmask an α-adrenergically-mediated vasoconstriction and facilitate the return of wave reflection in late systole rather than in diastole, thereby increasing the Aix. The reduced arteriolar lumen observed with β-blockers may be not only functional (vasoconstriction) but also structural. Indeed, small arteries of patients receiving long-term administration of atenolol exhibited unchanged media/lumen ratio and a stiffer wall, whereas small artery walls from patients treated with an angiotensin receptor blocker had a reduced media/lumen ratio, with no change in arterial stiffness. Second, the slowing of heart rate provides an opportunity for the reflected wave to appear in late systole. Third, because of the steep fall of the impedance modulus curve in the low-frequency range, lowering heart rate, that is, the fundamental frequency, causes the heart and arterial system to interact less efficiently. All 3 factors contribute to an impedance mismatch between the heart and arterial system, raising central PP. The CAFE study showed that the reduction in central SBP and PP was higher in the amlodipine- than in the atenolol-based treatment group, despite similar reduction in SBP and PP at the brachial level. However, because central PP and Aix were not measured at baseline in the CAFE study but only after one year of treatment, it is not possible to determine the amplitude of central PP and Aix reduction, thus its influence of CV events. In the LIFE study, the achieved reduction in brachial PP was central PP and Aix reduction, thus its influence of CV events.

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Arterial Stiffness in Hypertension

Laurent and Boutouyrie

5


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