

Influence of Age, Risk Factors, and Cardiovascular and Renal Disease on Arterial Stiffness: Clinical Applications

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Age is the main clinical determinant of large artery stiffness. Central arteries stiffen progressively with age, whereas peripheral muscular arteries change little with age. A number of clinical studies have analyzed the effects of age on aortic stiffness. Increase of central artery stiffness with age is responsible for earlier wave reflections and changes in pressure wave contours. The stiffening of aorta and other central arteries is a potential risk factor for increased cardiovascular morbidity and mortality. Arterial stiffening with aging is accompanied by an elevation in systolic blood pressure (BP) and pulse pressure (PP). Although arterial stiffening with age is a common situation, it has now been confirmed that older subjects with increased arterial stiffness and elevated PP have higher cardiovascular morbidity and mortality.

Increase in aortic stiffness with age occurs gradually and continuously, similarly for men and women. Cross-sectional studies have shown that aortic and carotid stiffness (evaluated by the pulse wave velocity) increase with age by approximately 10% to 15% during a period of 10 years. Women always have 5% to 10% lower stiffness than men of the same age.

Age and Arterial Stiffness

Using various assessment techniques, an age-dependent increase in arterial stiffness in both healthy and diseased populations has been described. It has been shown that in vivo aortic stiffness decreases sharply with age in the first decade of life, reaching a minimum at 10 years of age, and thereafter increasing with age in both genders.¹ This age-dependent increase in central arterial stiffness is independent of mean blood pressure (BP) or the presence of other risk factors.² Using multivariate models, age is the major

Although large artery stiffness increases with age independently of the presence of cardiovascular risk factors or other associated conditions, the extent of this increase may depend on several environmental or genetic factors. Hypertension may increase arterial stiffness, especially in older subjects. Among other cardiovascular risk factors, diabetes type 1 and 2 accelerates arterial stiffness, whereas the role of dyslipidemia and tobacco smoking is unclear. Arterial stiffness is also present in several cardiovascular and renal diseases. Patients with heart failure, end stage renal disease, and those with atherosclerotic lesions often develop central artery stiffness. Decreased carotid distensibility, increased arterial thickness, and presence of calcifications and plaques often coexist in the same subject. However, relationships between these three alterations of the arterial wall remain to be explored. Am J Hypertens 2002;15:1101-1108 © 2002 American Journal of Hypertension, Ltd.

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clinical determinant of aortic stiffness, a finding confirmed in several populations in different countries.^{1,3,4}

The underlying basis for these age-dependent changes is still incompletely understood. Pathologically, fracture and fragmentation of the elastin fibers after repetitive stress cycles, with consequent dilation and stiffening have been observed.⁵⁻⁷ A more dynamic, cellular ionic basis for age-related changes in arterial compliance have also been described.⁸ Thus, 1) cytosolic-free calcium levels increase and free magnesium levels reciprocally decrease with age

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in circulating red cells, platelets, skeletal muscle, and brain⁸⁻¹¹; 2) direct magnetic resonance imaging (MRI)-assessed aortic distensibility/stiffness is closely related to steady-state intracellular free magnesium levels⁸; and 3) furthermore, when intracellular free magnesium levels are incorporated into a multivariate model, the age dependence of aortic stiffness is no longer significant.⁸

The effects of aging are different on proximal, predominantly elastic arteries, compared to distal, predominantly muscular arteries.^{5,12,13} Central arteries stiffen progressively with age, whereas stiffness of muscular arteries changes little with age.⁵ A number of clinical studies have analyzed the effects of age on aortic stiffness, mainly with the method of pulse wave velocity (PWV). The increase of central artery stiffness with age is responsible for earlier wave reflections and changes in pressure wave contours. Kelly et al¹⁴ observed that wave reflections were responsible for an increase of about 25% in pulse pressure (PP) between age 30 and 60 years. The effects of age on peripheral artery stiffness are less pronounced; it has been shown that the peripheral PWV (carotid-radial or femoral-tibial) changes with age are approximately two to three times less frequent than those of the central aorta.^{4,7} Similar results have been observed when local cross-sectional distensibility coefficients were evaluated at the sites of the carotid and femoral arteries of the same subjects. Carotid artery distensibility was strongly correlated with age, whereas no such correlation was observed at the site of the femoral artery.^{5,15}

Increase in aortic stiffness with age occurs gradually and continuously, similarly for men and women.¹⁵ Cross-sectional studies have shown that aortic PWV increases with age by approximately 0.1 m/sec per year (about 1%).³ Similar changes were observed at the site of the carotid artery.⁵ However, some studies have suggested that increase in large artery stiffness follows a nonlinear quadratic evolution, with a more pronounced increase after the age of 55 years.^{16,17} This result corroborates the well-known epidemiologic observation of an increasing prevalence of systolic hypertension, the main clinical manifestation of large artery stiffness, after the age of 55 years.¹⁸

Although large artery stiffness increases with age independently of the presence of cardiovascular risk factors or other associated conditions, the extent of this increase may depend on several environmental or genetic factors. Studies have shown that PWV increased less with age in populations with low salt diet than in those with high sodium chloride consumption.¹⁹ The role of other environmental factors is less documented. Breithaupt-Grogler et al²⁰ have shown that people with high garlic consumption had a less pronounced increase in arterial stiffness with age. We have recently shown that the relationship between age and aortic PWV was influenced by the angiotensin II type 1 (AT₁) genotypes,¹⁷ indicating that genetic variants may influence the development of arterial stiffness with age.

In the past, vascular stiffening and increase in systolic and pulse pressure have been considered as a part of normal aging and no treatment for these alterations has been proposed. However, although arterial stiffening is a common situation, it has now been confirmed that older subjects with increased arterial stiffness and elevated systolic and PP have higher cardiovascular morbidity and mortality.²¹⁻²⁵ Therefore, large artery stiffening can be considered as a marker of arterial age, and should be considered as a major risk factor for cardiovascular events.

Hypertension and Arterial Stiffness

In subjects with hypertension, the principal structural modification of the vessel wall is hypertrophy of the medial layer.^{12,26} In younger hypertensive subjects, the alterations of the mechanical properties result mainly from the elevated BP itself, as reduced carotid compliance and distensibility disappear in isobaric conditions.²⁷ However, in some other territories such as the femoral artery or even the thoracic aorta, intrinsic changes in stiffness (ie, increased stiffness in isobaric conditions) may be observed.²⁸ In subjects with hypertension, active mechanisms within the arterial wall are certainly involved because, at the site of peripheral muscular arteries such as the radial artery, diameter is unchanged despite the elevated BP, whereas in central arteries, the diameter is increased in proportion with the level of BP.²⁶

Among the elderly hypertensives, medial hypertrophy is associated with a considerable development of the extracellular matrix of the media and even of the adventitia. This histomorphometric pattern is associated with reduced compliance and distensibility independent of BP level.²⁹ Again, these changes are observed at the site of central, but not peripheral, arteries. Finally, both with aging and hypertension, endothelium alterations are noted. Although endothelium alterations may differ markedly in the hypertensive and in the aging process according to the topography of the vessels,^{30,31} a major role is attributed to changes in nitric oxide (NO) production or release. The NO release is of particular importance for peripheral muscular arteries in which NO and vasoconstrictive compounds in relation with vascular smooth muscle cells are in constant interaction.^{30,31} The renin-angiotensin-aldosterone system (RAAS) activity may also play a key role in the regulation of arterial stiffness in hypertensives. We have shown that in hypertensives but not in normotensives, the angiotensin II type 1 (AT₁^{1166A/C})³² receptor and aldosterone synthase (CYP11B₂^{-344T/C}) gene variants³³ are significant determinants of arterial stiffness. These results suggest that neurohormonal systems, such as the RAAS may have synergistic effects with mechanical factors (increase in BP) on large artery's stiffness.

Effects of Hypertension and Age on Central and Peripheral Pressure Waveforms

Ejection of blood into the aorta generates a pressure wave that is propagated to other arteries throughout the body. This forward traveling (incident) pressure wave is reflected at all points of structural and functional discontinuity of the arterial tree, generating a reflected wave traveling backward toward the ascending aorta.¹² Incident and reflected pressure waves are in constant interaction and are summed up in a measured pressure wave. The final amplitude and shape of the measured PP wave are determined by the amplitude of the forward wave and the phase relationship (the timing) between the component waves. The timing of incident and reflected pressure waves depends on the PWV, the traveling distance of pressure waves, the level of reflection coefficients, and the duration of ventricular ejection. The desirable timing is mainly disrupted by increased PWV in relation to arterial stiffening. With increased PWV, the reflecting sites appear closer to the ascending aorta and the reflected waves occur earlier, being more closely in phase with incident waves in this area. The earlier return means that the reflected wave impacts on the central arteries during systole rather than diastole, thus amplifying aortic pressure during systole and reducing aortic pressure during diastole.^{12,26} This dual alteration of systolic and diastolic BP with a resulting increase in pulse pressure is observed during both the hypertensive and the aging processes, although there are important differences between the two clinical situations. With hypertension, there is, in the younger population, a persistence of the PP gradient, which is the reason that PP remains higher in peripheral than in central arteries, but with a resetting of the gradient toward higher values of mean arterial pressure.²⁶ This hemodynamic pattern is related to the normal amplitude of the forward pressure wave, whereas reflection coefficients are elevated as a consequence of arteriolar constriction.¹² On the other hand, with aging, the PP gradient tends to disappear, due to a more rapid stiffening with age of central, but not peripheral arteries, with a resulting increase in the amplitude of the forward pressure wave and the existence of low reflection coefficients. These differences in BP behavior in the hypertensive and the aging process may be due to a number of factors in addition to arterial stiffness. Most of them are combined in old hypertensive subjects. First, the timing of wave reflections is influenced by the characteristics of the reflection coefficients of the pressure wave, which are principally located at the origin of resistant vessels. It is important to note that the control of peripheral vascular resistance, and hence of small arteries, is modified with age and hypertension, particularly through endothelial or neurohumoral changes.¹² Second, the location of the same reflection sites may be substantially modified with aging and hypertension, in relation with the age- and pressure-induced increase in the caliber of arteries and

with the age-induced increase in the length of large vessels.^{12,28} Third, pathologic alterations may also produce reflection sites closer to the heart, as shown in the presence of calcified plaques, particularly at the site of arterial bifurcations (aorta; carotid and femoral arteries; origin of renal arteries).^{12,26,34} When examined together, these examples indicate that both increased arterial stiffness and alteration of wave reflections contribute independently to the predominant or selective increase of PP observed with age and hypertension and especially their combination.

Diabetes and Arterial Stiffness

Even among normal subjects, fasting blood glucose values are closely related to arterial stiffness, whether assessed on the basis of direct MRI-based measurements of aortic distensibility,⁸ or using more indirect computerized pulse waveform analysis of the radial artery³⁵—the higher the blood glucose, the stiffer (less distensible or compliant) the artery. These more recent findings were preceded by earlier observations of more obviously abnormal vascular stiffness among hyperglycemic diabetic individuals. Although hyperglycemia is a common feature in all diabetics, and although approximately 90% of clinical diabetes is of the type 2, non-insulin dependent form, type 1 and type 2 diabetes will be considered separately as certain etiologic and clinical differences may distinguish them.

Diabetes, Type 1

A number of studies have reported that type 1 diabetic patients have stiffer arteries than normal subjects.^{36–45} However, several major factors, such as the duration of the illness, the degree of obtained control under therapy, and the complications of the disease, may influence the effects of type 1 diabetes on large arteries. Lehmann et al³⁸ analyzed the aortic compliance in recent onset child patients. Their results contradicted reports in the literature and showed that the young type 1 diabetic patients evaluated within 1 year of diagnosis have aortas ranging up to 78% more distensible than their sex- and age-matched nondiabetic controls. On the other hand, Kool et al³⁹ reported reduced arterial distensibility only at the femoral artery level but not at the site of carotid and brachial arteries in uncomplicated diabetic adults. Ahlgren et al⁴⁰ reported increase of aortic and carotid stiffness in diabetic women but not in diabetic men. Similar results were reported more recently by Ahlgren⁴¹ who showed a significant correlation between aortic stiffness and duration of diabetes and autonomic dysfunction in diabetic women. Also, an Italian study⁴² showed that type 1 diabetes was characterized by diffuse arterial wall stiffening and thickening even in patients without any clinical vascular complications, showing that large artery stiffness and hypertrophy are early markers of vascular damage. More recently, Lambert et al⁴³ showed that acute hyperglycemia had no effects on the arterial wall properties, whereas an association between arterial stiffness and heart rate vari-

ability has been described by Jensen-Urstad et al.⁴⁴ Finally, when all the data published on this subject are considered, all but one of the studies showed a decrease of arterial distensibility in type 1 diabetic patients. These arterial abnormalities, which have been reported even in young patients, children and adolescents, seem to be more pronounced at the aortic and the lower limb levels, with a significant correlation with the duration of diabetes.

Diabetes, Type 2

Several studies showed an increase in arterial stiffness in type 2 diabetic patients, and positive correlations between arterial stiffness and free fatty acid and insulin levels.^{36,45-54} It was also found that arterial stiffness was best predicted on the basis of age and area under the blood glucose curve. These results suggested that noninvasive investigation of arteries may be useful in the evaluation of presymptomatic stages of atherosclerosis in diabetes. Lehmann et al³⁸ analyzed the aortic compliance in type 2 diabetic patients using measurements of PWV. Their results support findings by other groups and showed that type 2 diabetic patients have significantly stiffer aortas than their age- and sex-matched nondiabetic controls. Megnien et al⁵⁰ studied the effects of non-insulin-dependent diabetes mellitus on the physical properties of the brachial artery in men. Their results showed that in comparison to control subjects, diabetic patients had lower operating and isobaric compliance. In the control and diabetic groups, fasting glucose correlated negatively with measured and isobaric compliance. Elsewhere, Amar et al⁵¹ studied the influence of glucose metabolism on carotid-femoral PWV in untreated hypertensive patients with elevated waist/hip ratio. Their results showed higher PWV values in diabetics and glucose intolerant patients, compared to those with normal glucose levels. A positive correlation between PWV and fasting glycemia was noted.

On the whole, the published data showed higher stiffness in type 2 diabetic patients and also in normal subjects with a positive family history of diabetes.⁵²⁻⁵⁴ Associations between PWV and fasting glucose and insulin levels, as well as insulin resistance, have been described. One study reported that these arterial abnormalities are more evident at the aortic and the lower limb levels than in the upper limbs. More specific studies, which take into consideration the duration of the disease, its treatments, and the degree of control obtained under treatment, are needed to understand the mechanisms involved between arterial stiffness and type 2 diabetes. Studies should also be extended to the problem of insulin resistance and its treatment.

Dyslipidemia and Arterial Stiffness

On the basis of experimental and clinical studies, it has been reported that excess cholesterol substantially alters the endothelial function, leading to a decreased relaxation of the arterial vessels.⁵⁵ The defect has been described

mainly in atherosclerotic patients but also in asymptomatic subjects with hypercholesterolemia.⁵⁶ Whether this abnormality is associated with an increased stiffness of the arterial wall in humans remains to be demonstrated and for the moment the results of the literature are controversial.

Data from animals have shown an unexpected increase in aortic distensibility and compliance at an early stage of diet-induced experimental atherosclerosis, which subsequently decreased (ie, the aortas became stiffer) as atheroma progressed in the later stages of the disease.^{57,58} These findings have been partly confirmed by other investigators who reported a decrease of aortic distensibility in animals exposed to grossly elevated plasma cholesterol levels with severe experimental atherosclerosis.^{59,60}

Lehmann et al⁶¹ investigated young patients with heterozygous familial hypercholesterolemia and sex- and age-matched normocholesterolemics. They showed that patients with familial hypercholesterolemia had significantly more distensible aortas than the control subjects, with significant positive correlations between compliance and cholesterol, low-density lipoprotein cholesterol (LDL) and duration of disease, and a negative correlation between aortic compliance and high-density lipoprotein cholesterol (HDL). Interestingly, the same researchers^{62,63} showed that adults with familial hypercholesterolemia had significantly less distensible aortas than normocholesterolemics, with an inverse correlation between LDL-cholesterol and aortic distensibility in pooled data, age and LDL-cholesterol being the best independent predictors of aortic distensibility. Some studies reported increased rigidity of the aortic wall in groups of hypercholesterolemic subjects.⁶⁴ Giannattasio et al⁶⁵ observed a marked reduction in radial artery compliance in subjects in a small population of patients with familial hypercholesterolemia. Interestingly in that study, a long-term treatment of hypercholesterolemic patients with a statin was able to increase arterial compliance. However, studies from different populations^{66,67} failed to demonstrate any association between aortic stiffness (evaluated with the PWV) and total plasma cholesterol. In these population studies, the different fractions of lipoproteins were not evaluated. Kupari et al⁶⁸ even described a negative relationship between arterial stiffness and LDL-cholesterol levels.

Effects of Smoking on Arterial Stiffness

Although smoking is known to alter the arterial wall, particularly the endothelial function, and to accelerate atheromatosis in several arterial territories, little is known about the influence of tobacco consumption on arterial stiffness. Failla et al⁶⁹ showed that in smokers without any overt cardiovascular disease, acute cigarette smoking reduced distensibility in both medium and large arteries. It has also been demonstrated that cigarette smoking increased PWV in both normotensive and hypertensive

subjects.⁷⁰ The acute effects of smoking were also investigated in chronic smokers by several investigators.^{71–75} All of these studies showed that acute smoking significantly decreased carotid and brachial distensibility, and increased BP. However, no basal differences related to long-term effects of smoking were found, compared to nonsmokers.^{71,76} In middle-aged women, no association between aortic PWV and history of smoking was observed.

Arterial Stiffness in Heart Failure Patients

In congestive heart failure (CHF), several researchers showed, through the use of invasive methods, the presence of abnormalities of large conduit vessels, and more specifically that physical properties of the aortic wall are significantly altered.⁷⁷ In fact, conduit artery distensibility affects the pulsatile component of afterload and contributes to impaired left ventricular function. This may be partly reflected by the relative reduction of BP with heart failure, where as PWV remains high. Nonetheless, few studies using noninvasive methods have been conducted to evaluate the role of large arteries in heart failure, and mostly to determine whether comparable abnormalities to those seen at the ascending aorta are present in other parts of the arterial tree.

All but two of the studies showed that arterial compliance and distensibility evaluated at the aortic, carotid, iliac, or brachial artery levels are impaired in different populations of patients with CHF.^{78–80} In addition, hyperemic flow was associated with increases in distensibility in healthy subjects but not in CHF patients, whereas sublingual glyceryl trinitrate induced similar effects in both groups.⁸⁰ These results point to the role of the endothelium on the arterial properties in CHF and imply that endothelium derived relaxing factor mediated increases in distensibility are impaired in CHF patients. Concurrently, Giannattasio et al⁸¹ showed that at the radial artery level, baseline compliance is altered in patients with severe CHF but not in those with mild CHF. However, the postischemic increase in compliance was blunted in both mild and severe CHF, suggesting that arterial compliance and its modulation are impaired in CHF. The same investigators reported that the impaired arterial compliance occurring in CHF was increased by treatment with angiotensin converting enzyme (ACE) inhibitors.⁸² They concluded that addition of an ACE inhibitor could counteract the adverse effects of reduced compliance in patients with CHF such as increased cardiac work and oxygen consumption, decreased coronary perfusion, and altered baroreflex.

The exact mechanism of these alterations is not clear. Further studies are needed to assess the mechanisms of increased arterial stiffness in patients with heart failure (altered flow dilatation, increased activity of the sympathetic system).

End-Stage Renal Diseases and Arterial Stiffness

Clinical and epidemiologic studies have shown a high prevalence of systolic hypertension in end-stage renal disease (ESRD). The principal factor responsible for increased systolic BP and PP in ESRD patients is increased arterial stiffness with increased PWV and early wave reflections.^{83,84} Indeed, in comparison with age- and mean blood pressure-matched nonuremic patients, the arterial stiffness is greater in ESRD, especially in younger uremic subjects. The stiffening is more pronounced in the aorta than in peripheral arteries. It has recently been shown that in ESRD patients aortic stiffness was an independent risk factor for total mortality and cardiovascular morbidity and mortality.⁸⁵ Increased arterial stiffness was found to be associated with the presence of arterial calcifications and a low HDL-cholesterol level, but not with other metabolic or hormonal disturbances commonly observed in ESRD.⁸⁴ Several studies that include ESRD patients indicate that sodium overload may induce arterial stiffening independently of BP changes. In ESRD patients, a positive relationship between interdialytic body weight gain and aortic PWV was observed, supporting the potential role of sodium excess. Besides the increase in peripheral systolic BP and BP, the most obvious consequence of arterial stiffening in ESRD patients is an early return of wave reflections to the aorta and the disappearance of aortic-to-peripheral pressure amplification.⁸⁶ This phenomenon, which normally occurs after the sixth decade, appears already during the fourth decade in ESRD patients and means that for a similar brachial systolic BP, the aortic systolic BP is higher in ESRD patients than in nonuremics. The second factor associated with an early return of wave reflections in ESRD patients is a shorter effective length of the arterial tree.^{86–88} This is related to a shorter body size, principally shorter body height, resulting from malnutrition and growth retardation frequently observed in azotemic children and adults with nephropathies starting in childhood. With a comparable arterial stiffness and peripheral resistance, ESRD patients with short body height have an increased effect of wave reflections on aortic pressure. Low body height was also found to be associated with cardiovascular risk in men and women in the general population. Whether arterial stiffness and altered wave reflection occur at the early phase of renal diseases still remain unknown.

Atherosclerotic Alterations and Arterial Stiffness

The best example associating atherosclerosis and arterial stiffness (arteriosclerosis) is observed in patients with arteriosclerosis of the lower limbs.^{89,90} Increased systolic and PP are commonly observed in these patients, whereas mean arterial pressure, vascular resistance, and ventricular

ejection remain largely within the normal range. Systemic and forearm arterial compliance are significantly reduced. In these subjects, increased PP is significantly and independently associated with the reduction in the vasodilating arteriolar properties of the diseased limbs, as evaluated with plethysmography.⁸⁹ Coronary ischemic disease has been found to be substantially associated with increased aortic stiffness.⁹¹ Although an increased incidence of elevated systolic BP was not reported in populations of subjects with ischemic heart disease, these subjects frequently only have a wide PP and decreased diastolic pressure-time index in association with the already mentioned aortic stiffening. Experimentally, decreased aortic compliance participates in and aggravates the myocardial ischemia observed in the presence of stenosis of the coronary artery.⁹²

Stenosis of the internal carotid artery is frequently associated with systolic hypertension.^{93,94} In subjects with carotid endarterectomy, a significant increase in systolic BP variability is also observed, particularly during the night.⁹⁵ Decreased carotid distensibility, increased arterial thickness, and presence of calcifications and plaques often coexist in the same subjects.⁹³⁻⁹⁵ However, the relationships between these three alterations of the arterial wall, that is, atheromatosis (plaques), hypertrophy (increased media thickness), and stiffness (decreased compliance), remains to be explored.

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