

Hypertension and Vascular Aging

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ABSTRACT

Hypertension syndrome is a complex set of hemodynamic maladaptations that include stiff central arteries with pressure amplification, arteriolar constriction, microcirculatory rarefaction, metabolic abnormalities, cardiac hypertrophy and increased blood pressure variability. Cardiovascular aging in hypertension is accompanied by isolated systolic hypertension and an increased pulse pressure due to the increased central arterial stiffness, and patients with this malady have higher cardiovascular morbidity and mortality rates. Systolic hypertension causes endothelial dysfunction and atherosclerosis/arteriosclerosis, so that the aortic compliance is reduced and the small resistance arteries are constricted with inward eutrophic remodeling. Central arterial stiffness increases the SBP variability and also the blunt aortocarotid baroreflex, which can cause orthostatic hypotension. (Korean Circulation J 2006;36:477-481)

KEY WORDS : Hypertension ; Aging ; Arterial stiffness ; Atherosclerosis.

Introduction

The human arterial system extends from the capillaries to the aorta, and these vessels have substantially expanded container volumes and continuously increased vessel wall/diameter ratios, and increased smooth muscle content and a decreased elastin content as the system progresses from the smaller vessels to the largest vessels (Table 1).

Chronic hypertension is characterized by an increase in the peripheral resistance, and this is due to an increase in mural thickness on one hand and to arterial wall rigidity on the other. Thickening and rigidification are the result of increases in both the smooth muscle cell mass and the absolute amount of matrix protein. These structural changes result in decreased compliance. Age-related change is generally recognized as resulting from cell damage.¹⁾ As the person gets older, the cardiac mass increases while the cardiac efficacy decreases. Hypertrophy of the heart is accompanied by a change in the enzymatic property of myosin. The walls of the greater arteries simultaneously become thicker, more rigid and less compliant, with hypertrophy of the smooth muscle cells being an essential component of this vas-

cular wall thickening. At the same time, the collagen fraction and the amount of collagen-bound calcium increase. The elastic component decreases, at least relatively, and the elastin-collagen ratio clearly diminishes with age. The final result of all this is reduced permeability of the tunica media, and it facilitates the accumulation, in the subendothelium, of lipidic and/or proteinic compounds that originate from the plasma; this constitutes a link between aging and the atheromatous processes.²⁾

Vascular Change of Aging Arterial Wall in Hypertension (Table 2)

All segments of the vascular system are affected by aging. In elderly subjects, the pressure-volume curve shifts to the right, and compliance is decreased. Aging large arteries are elongated and tortuous and have an enlarged lumen and a thickened wall, with the thickening mainly affecting the intima and the media.³⁾ As their size increases, blood velocity also decreases. The reduction in compliance, which is independent of the blood pressure level, is most probably due to structural changes in the vessel wall. Functionally, the aged vessels show increased endothelial permeability and a reduced nitric oxide-dependent vasodilator response to acetylcholine.⁴⁾ The vasodilator responses to α_2 -adrenoceptor agonists are also clearly attenuated because of the reduced number and affinity of specific receptors.

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Table 1. The features of the main arterial compartments in human

	Number	Diameter	Wall thickness	Predominant structure	Function
Aorta	1	2-3 (cm)	2-3 (mm)	Elastin	Conduction
Large and midsized arteries	10 ²	3-8 (mm)	0.5-1 (mm)	Muscle	Distribution
Small arteries	10 ³	0.5-3 (mm)	0.5-1 (mm)	Muscle	Distribution
Arterioles	10 ⁶	10-100 (um)	10-100 (um)	Muscle	Resistance
Capillaries	10 ¹⁰	4-10 (um)	1-3 (um)	Endothelium	Exchange

Table 2. Effect of aging on vascular structural and the functional changes in hypertension

Vascular changes	
Increase	Decrease
Intima-media	Elastin
Subendothelial collagen	Arterial distensibility
Elastin fragmentation	NO release
Preteoglycans	SOD activity
MMP activity	B-Adrenergic-mediated
Proliferation of VSMC	vasodilation
Pulse wave velocity	
Total peripheral resistance	
Endothelial permeability	
Inflammatory marker	

MMP: matrix metalloproteinases, VSMC: vascular smooth muscle cell, SOD: superoxide dismutase

Atherosclerosis and arteriosclerosis

In chronic hypertension, the endothelial cells may be irregular in shape and have increased height; there may be migration and/or proliferation of vascular smooth muscle cells with infiltration into the subendothelial space and exaggerated deposition of collagen, elastin, and proteoglycans, along with an abnormal abundance of leukocytes and macrophages. Numerous substances are involved in the inflammatory and/or atherosclerotic processes such as adhesion molecules, matrix metalloproteinases, transforming growth factor- β , and others too, such as proinflammatory cytokines, and all these proteins and organic chemicals are also more abundant in aging arterial intima. On the other hand, degenerative stiffening of arteries is sometimes called arteriosclerosis to differentiate it from atherosclerosis, which is the occlusive result of endovascular inflammatory disease, lipid oxidation and plaque formation. At a cellular level, arteriosclerosis is associated with structural changes in the central arteries, including the loss of elastin and increased extracellular matrix deposition of collagen, fibronectin and other structural proteins.⁵⁾

Aging and microcirculation

Aging is associated with enhanced endothelial permeability to macromolecules and with abnormalities in the aortic microcirculation, including the vasa vasorum that's located in the adventitia. A major consequence of these endothelial functional abnormalities is

the accumulation of macromolecular material in the media of the large arteries. It is also likely that abnormal penetration of macromolecules, including lipoproteins from either the luminal or antiluminal sides of the aorta, contributes to atherogenesis. The endothelial permeability alterations that accompany aging results in increased pulse pressure owing to the increased rigidity of the large vascular conduits, with both the "resistance arteries" and capillary networks being affected.⁶⁾ The endothelial layer reorganization that develops in response to the traumatic effects of sustained arterial hypertension during aging may well lead to the enhanced permeability to macromolecules. Such shear stress phenomena have even been demonstrated in the proximal renal tubular epithelium, and these effects could well contribute to functional deterioration of the kidney with aging.⁷⁾

What mechanical forces work for arterial aging?

The arterial wall is subject to two types of mechanical force: shearing stress at the blood-wall interface that's directly due to the blood flow velocity profile, and the mural or tangential tension that's due to pressure. The shearing stress is determined by the velocity gradient on the vessel wall. At a given blood flow volume, the smaller the vessel diameter, the greater is the shearing stress. Because arteries at bends or branch points cause changes in the velocity profile, at the distal edge of a collateral ostium or at the apex of a bifurcation, shearing stresses are higher and endothelial turnover increases.⁸⁾

At the wall, pressure becomes converted into mural, tangential or circumferential tension. Laplace's law states that this tension is proportional to the pressure and the vessel's radius, and it is inversely proportional to the mural thickness. In elastic vessels, the increase of pressure increases with the vessel radius and the artery becomes functionally more rigid at higher pressure.

Large Arterial Aging and Arterial Stiffness

Aortic wall composition

Collagen fiber and calcium are accumulated in the artery with increasing age, and the intima thickening and denaturation of the media contribute to the arterial stiffness. The role of arteriosclerosis in systolic

hypertension is that the aorta widens and becomes thicker and stiffer, leading to reduced elasticity and a wide pulse pressure as end-stage manifestation of this condition.⁵⁾ Acute increases in blood pressure stretch the load-bearing elastic lamellae, making the arteries functionally stiffer. Hemodynamically, the age-related increase in the SBP and widening of the pulse pressure generally indicates increased central arterial stiffness (Fig. 1). A mechanism leading to a wide central pulse pressure is pressure augmentation from reflected waves. In young people, the primary reflected wave returns to the central aorta in diastole, where it augments coronary and cerebral perfusion. However, if the arteries are stiff, the primary reflected wave arrives back at the aortic root during late systole, where it summates with the incident wave, which adds to the central pulse pressure and cardiac afterload.⁹⁾

Arterial compliance and blood pressure

As a result of the dual function of the arteries, i.e., the conduit and cushioning functions, the arterial pressure has two components: the steady component that is characterized by the mean blood pressure, and the pulsatile component that is characterized by the pulse pressure. Arterial compliance mostly depends on the arteries' intrinsic elastic properties, and arterial compliance is a determinant of the propagation speed of the pulse pressure wave. Decreased arterial compliance is responsible for both an increase in the incident pressure wave and the higher effect of reflected pressure waves. This increases the systolic pressure and the ventricular afterload, and so it generates left ventricular hypertrophy. The arterial structural changes that accompany the aging process result in a loss of distensibility and compliance. Arterial compliance is reduced in essential hypertension as well as in secondary hypertension, and so the age-

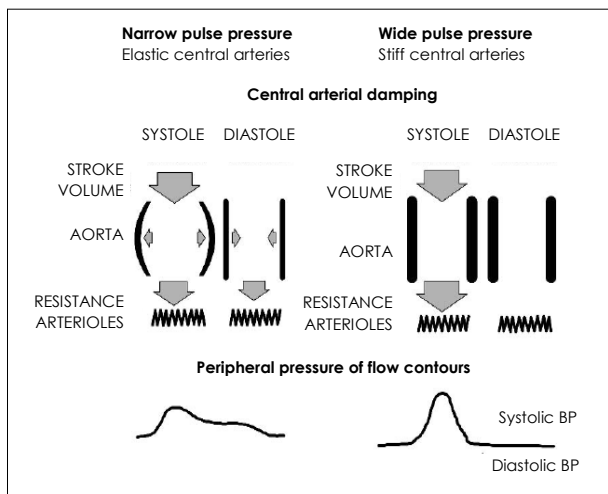


Fig. 1. Central arterial damping and the peripheral pulse pressure (adapted in part from Reference 15).

related structural changes of the arterial wall are accelerated.

Large arterial aging and isolated systolic hypertension

The abnormalities of the large arterial conduits are responsible for isolated systolic hypertension and an increased pulse pressure, and there are potential consequences of these abnormalities on the left ventricle lying upstream as well as on the arteries that are responsible for the peripheral resistance and the micro-circulation networks downstream. Enhanced contractility of the aortic tissue in response to angiotensin II could contribute to increased rigidity of this conduit vessel, leading to isolated systolic hypertension. The systemic hypertension accelerates the age-related vascular hypertrophy and the increased systolic pressure and pulse pressure. In turn, the elevated pressure is a stimulus for further stiffness and hypertrophy of the vessel wall, so that a more or less rapidly progressing vicious circle is established.

Small Artery Remodeling in Hypertension

Small blood vessels, particularly the small arteries with lumen diameters of 150-300 microns and the larger arterioles with lumen diameters of 50-150 microns, are the most important location of the arterial bed that undergoes changes resulting in the increased peripheral resistance that characterizes elevated blood pressure. The media of the vessel wall was significantly thickened in the hypertensive rats, and the media/lumen ratio (M/L) was also increased.¹⁰⁾ In arterioles, decreases in the density of the blood vessels (rarefaction) and in the vasomotion amplitude may play a more important role than the reductions of lumen diameter (Fig. 2). Maladaptive accommodation of arteriolar constriction may amplify the systemic hemodynamic

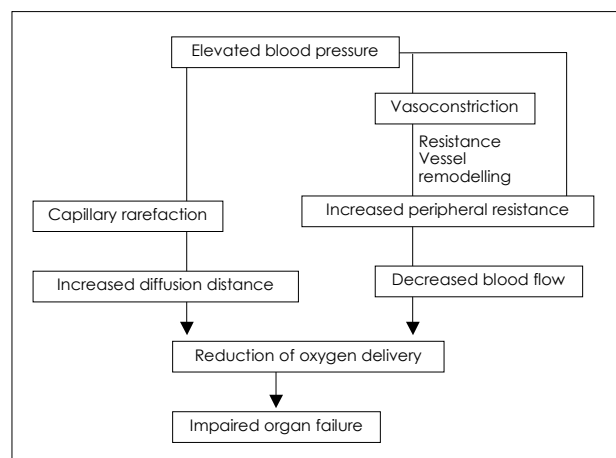


Fig. 2. Relationship between capillary rarefaction and high blood pressure, and their impact on organ function.

Table 3. Clinical manifestation of systolic hypertension (adapted in part from Reference 15)

Circulatory component	Pathophysiologic changes	Clinical manifestations
Heart	Afterload	LVH Diastolic dysfunction Heart failure
	Coronary reserve	Exercise intolerance Ischemia
Aorta/central arteries	Stiffness	Pulse pressure (SBP+ DBP) Blood pressure variability
Peripheral arteries	Normal or diameter	None
	Normal or stiffness	
Arterioles	Pulse pressure amplification (variable)	Spurious systolic hypertension (variable)
	Systemic vascular resistance	Mean arterial pressure (SBP+ DBP)
	Wave reflection	Augmentation index
Microcirculation	Pressure overload	Stroke
	Capillary surface area	Chronic kidney disease Insulin resistance Albuminuria Cerebral arteriosclerosis

DBP: diastolic blood pressure, SBP: systolic blood pressure

abnormality because the relative capillary underperfusion stimulates excitatory muscle and kidney chemoreflexes, which in turn increase the sympathetic nervous tone and blood pressure.

Hypertension is known to be associated with an increase in the wall/lumen ratio (W/L) of the resistance arteries. Growth, eutrophic remodeling and changes in arterial distensibility can all contribute to an increase W/L. Wall stress may stimulate growth, whereas remodeling and/or reduced distensibility may be the result of prolonged contraction. Vascular structural alterations in the small resistance arteries of patients with essential hypertension (EH) are mostly characterized by inward eutrophic remodeling. Adrenergic mechanisms may have a relevant role in the development of eutrophic remodeling in the small vessels of humans.¹¹⁾ Increased pulse pressure and an increased M/L ratio of small-artery structures in hypertension were significantly associated with the occurrence of cardiovascular events.

Target Organ Damage

The cardiac afterload (and its three major components: MAP, central arterial impedance or stiffness, and central systolic pressure augmentation) is increased in those patients with systolic hypertension. The increased load leads to left ventricular hypertrophy and increased ventricular stiffness, and both of these have been shown to be more prevalent and further advanced in the pe-

ople with increased arterial stiffness, decreased aortic distensibility or decreased exercise tolerance.¹²⁾ Reductions in aortic compliance have a deleterious effect on coronary blood flow and ischemic thresholds. Aortic stiffness also correlates with the severity of carotid plaques and the degree of renal failure.¹³⁾ In further support of this comprehensive model, wide pulse pressure is correlated with albuminuria, and this is a marker of glomerular capillary hypertension and renal microcirculatory damage (Table 3).

Endothelial Dysfunction(ED)

Hypertension has a direct influence on the vascular function that is independent of other cardiovascular risk factors. The twenty-four-hour ambulatory systolic BP was significantly, inversely related to flow-mediated responses.¹⁴⁾ Endothelial dysfunction does not seem to occur in middle-aged white coat hypertensive patients who are without other cardiovascular risk factors. The left ventricular hypertrophy that's associated with hypertension has an additional negative effect on endothelial function in hypertensive patients. A dysfunctioning endothelium due to the reduced availability of NO and the increased production of oxidative stress are considered to be early indicators of atherothrombotic damage and also cardiovascular events. Once the oxidative stress production becomes detectable, the availability of NO is totally compromised. Essential hypertension represents a mere acceleration of the ch-

anges induced by aging on the endothelial function.

Blood Pressure Variability and Orthostatic Hypotension

Increased central arterial stiffness is positively correlated with SBP variability and the white coat effect.¹⁵⁾ Central arterial stiffness (the thoracic aorta, carotid and femoral arteries, but not the brachial artery) correlates negatively with arterial baroreflex sensitivity, especially when the blood pressure increases acutely.¹⁶⁾ The mechanism of this effect is believed to be aortocarotid baroreflex blunting that is caused by physical restriction of the mechanoreceptor sensors via the stiffened central arterial walls. The heart hypertrophies and stiffens in parallel with the central arteries, leading to reduced cardiopulmonary baroreflex sensitivity with age. The net results of the blunting of both baroreflexes include a diminished capacity to buffer acute increases in the SBP and an increase in the chronic sympathetic nervous outflow, which increases the MAP and the SBP. Reflex haemodynamic responses to orthostatic stress are attenuated with ageing, and the extent of attenuation increasing with advancing age. In 15-20% of individuals aged >65 years, the attenuation may be so marked that there is an excessive fall of blood pressure (BP) upon assuming an upright posture, and this is sufficient, on occasions, to cause symptomatic cerebral hypoperfusion: this is known as 'ageing-related' orthostatic hypotension, and it is a major risk factor for morbidity and mortality.¹⁷⁾

Conclusion

Hypertension is a complex, interlinked hemodynamic syndrome that includes stiff central arteries, arteriolar constriction, microcirculatory rarefaction, metabolic abnormalities, cardiac hypertrophy and increased blood pressure variability. Cardiovascular aging in hypertension is accompanied by isolated systolic hypertension and an increased pulse pressure via the increased central arterial stiffness, which is correlated with higher cardiovascular morbidity and mortality. Future research efforts should try to find the association of arterial aging and hypertension by investigating such things as risk factor characterization and genetic polymorphism. Life style changes or pharmacological intervention have been shown to have favorable effects

on the arterial structure and function in human.

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