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## Arterial Elasticity in Cardiovascular Disease: Focus on Hypertension, Metabolic Syndrome and Diabetes

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### Abstract

Arterial stiffness is an independent risk factor for premature cardiovascular morbidity and mortality that can be evaluated by noninvasive methods and can be reduced by good clinical management. The present chapter examines the association between arterial stiffness and cardiovascular risk factors including hypertension, metabolic syndrome, diabetes, advanced renal failure, hypercholesterolemia and obesity. The mechanisms responsible for the structural and functional modifications of the arterial wall are also described. We deal with parameters related to arterial compliance, focusing on two of them, pulse wave velocity and the augmentation index, useful in rapid assessment of arterial compliance by the bedside. Data that highlight the role of aortic pulse wave velocity and the augmentation index as independent factors in predicting fatal and nonfatal cardiovascular events in different populations are briefly presented. A number of lifestyle changes and traditional antihypertensive agents that improve arterial compliance are finally discussed. Novel therapies, such as statins, thiazolidinediones, phosphodiesterase inhibitors and inhibitors or breakers of advanced glycation end product cross-links between collagen and elastin hold substantial promise.

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The principal function of the arterial system is to deliver an adequate supply of blood to the tissues and organs. In performing this conduit function, the arteries transform the pulsatile flow generated by ventricular contraction into a continuous flow of blood in the periphery. This latter cushioning function is dependent on the mechanical properties of the arterial wall. Arterial compliance depends on the structure and function of the vessel wall.

## Arterial Wall and Arterial Compliance

### *Arterial Wall*

The arterial wall is formed by endothelium, intima, media and adventitia. The endothelial basement membrane (BM) is the main support for attachment of endothelial cells and provides a filtering mechanism due to strong anionic charges of its matrix. The extracellular matrix (ECM) consists of collagen, elastin, proteoglycans (glycosaminoglycans), hyaluronan and structural adhesive glycoproteins. All these components are under the control of metalloproteinases.

The endothelial cells and BM along with ECM are the first defense mechanism against various toxic stimuli: aldosterone, LDL cholesterol, viruses and so on.

Therefore, ECM is the first layer that is affected by the process of atherogenesis. Later, each layer will be affected by these injurious stimuli. We will briefly describe the ECM components.

### *Collagen*

Collagen is the most abundant protein. The collagen molecule is formed by three polypeptide chains, which intertwine to form triple-helical rope-like collagen fibrils. These fibrils are cross-linked by hydroxyl groups between alpha chains (a major contributor to their tensile strength) to form the collagen fiber. These fibers, in turn, form collagen bundles. Gaps in the collagen fibril give the cross-banding appearance of type I and II collagen fibers at a characteristic length of 67 nm when viewed by electron microscopy. In type III collagen there is a structurally beaded appearance instead of the characteristic cross-banding appearance observed in type I and II collagen. The physical and tensile strength of collagens is typified by collagen type I (having the tensile strength of steel), which predominates in bones, tendons, skin, and mature scars, while type II collagen is thinner and predominates in cartilage, vitreous humor and nucleus pulposus. Type III collagen is found in organs requiring more plasticity such as blood vessels, heart, gastrointestinal tract, uterus, and the dermis. Types I, II and III collagen are the fibrillar-interstitial collagens and are the most abundant collagen types. They are important in diabetic remodeling fibrosis within the myocardium, the tubulointerstitium of the kidney, the intima in atherosclerosis, dermatopathy, interstitial changes within the retina (retinopathy), and possibly the neuronal unit of neuropathy. In contrast, collagens IV, V, and VI are nonfibrillar or amorphous and are found in BMs and interstitial tissue.

One very unique feature of type IV collagen is the presence of 7–8 cysteine residues, which are involved in intra- and intermolecular disulfide bonds, which aid in the stabilization of this polymer. This presence of cysteine in type

IV collagen is in contrast to mature fibrillar collagens types I, II and III, as they lack a cysteine moiety. Type IV collagen is found exclusively in BM [1–3].

#### *Elastin*

Elastin is known to provide support and elasticity. This elasticity is important for many tissues and organs such as the blood vessels, heart, skin, lung, and uterus. Elastin is a 70-kDa glycoprotein and constitutes the central core of elastic fibers. It is cross-linked, but unlike most other proteins it does not form definite folds but rather oscillates between different states to form random coils. It is this cross-linked, random-coiled structure of elastin that determines the capacity of the elastic network to stretch and rebound.

Elastin provides an elastic molecular rebound capacity to the ECM and this is why there is a distinct internal and external elastic lamina on either side of the medial vascular smooth muscle layer of the arterial vessel wall [1–3].

#### *Proteoglycan*

Proteoglycan (PG) is found within the intima. It is synthesized primarily by the vascular smooth muscle cell and in BM by the endothelium. PG consist of core protein(s) covalently linked to one or more highly sulfated polysaccharide chains, called glycosaminoglycans. These molecules are highly diverse with multiple combinations of core proteins and polysaccharide chains. Examples are: heparan sulfate proteoglycans, chondroitin sulfate proteoglycans, keratan sulfate proteoglycans, and dermatan sulfate proteoglycans [1–3].

#### *Hyaluronan*

Hyaluronan is a huge molecule formed by disaccharides stretched end-to-end, while lacking a core protein. It binds large amounts of water and forms a viscous hydrated gel, which gives the ECM turgor and allows it to resist compressive forces. Because of this unique ability it is found in abundance in cartilage of joints as it provides resilience and lubrication. It serves as a ligand for core proteins and is often a backbone for large proteoglycan complexes. It facilitates cell migration and inhibits cell-cell adhesion. Hyaluronan is increased in atherosclerotic plaque erosion and is decreased in the vulnerable thin-cap atheroma associated with plaque rupture [1–3].

#### *Structural-Adhesive Glycoproteins*

Fibronectin forms a primitive matrix that allows the initial organization to be replaced by the definitive, organ-specific matrix. Fibronectin is a multifunctional adhesive protein whose primary function is to attach cells to a variety of matrices. Structurally, it consists of two polypeptide chains held together by two disulfide bonds. In addition to providing structural support it is associated with cell surfaces and BMs.

Laminin is the most abundant glycoprotein in BMs. This structural-adhesive glycoprotein binds to cells, proteoglycans, and type IV collagen. Laminin is a hetero-trimeric polypeptide and appears as a cross-like structure with a single central polypeptide A chain and two flanking polypeptide B chains. This adhesive glycoprotein is felt to be important in cellular alignment [1–3].

#### *Metalloproteinases and Their Inhibitors*

Collagen is maintained under the control of a group of zinc dependent, redox sensitive endopeptidases, named metalloproteinases. There is a delicate balance between the tearing down, rebuilding, tailoring and remodeling of the collagens within ECM. Also there is a delicate balance between metalloproteinases and their inhibitors. In physiological conditions, homeostasis is achieved. But, when the balance is broken, metalloproteinases degrade collagen and hydrolyze elastin, which results in rupture of arterial wall vulnerable plaques [1–3].

#### *Systolic Hypertension, Wide Pulse Pressure, Central Artery Stiffness and Arterial Compliance*

Systolic hypertension results principally from increased aortic and central arterial stiffness, although peripheral vasoconstriction also contributes [4].

The clinical hallmark of systolic hypertension is a pattern of wide pulse pressure (PP). PP is defined as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). In young healthy people the elastic recoil of proximal aorta and large arteries dampens the impact of pulsatile flow (narrow PP) by retaining a fraction of each cardiac stroke volume during systole and then delivering this retained volume in diastole.

When central arteries stiffen with age and hypertension, the full stroke volume is delivered through the resistance arterioles during systole because there is no elastic recoil (compliance) of the aorta. As a result, the PP widens and the SBP rises, independent of cardiac output or systemic resistance [4–7].

The arterial stiffness is altered primarily in association with increased collagen content and alterations of extracellular matrix and calcification of the arterial wall [9]. Arterial stiffness is one of the principal factors opposing left ventricular ejection. Arterial stiffening increases left ventricular afterload and alters the coronary perfusion and is a strong independent factor associated with morbidity and mortality, in the general population as well as in people suffering from cardiovascular disease and chronic renal failure [4–7].

Compliance defines the capacitive properties of central arteries, whose role it is to dampen pressure and flow oscillations and to transform pulsatile flow and pressure in arteries into a steady flow and pressure in peripheral tissues. Stiffness is the reciprocal value of compliance [4–8].

## **Assessment of Arterial Stiffness: Measurement of Pulse-Wave Velocity and Augmentation Index**

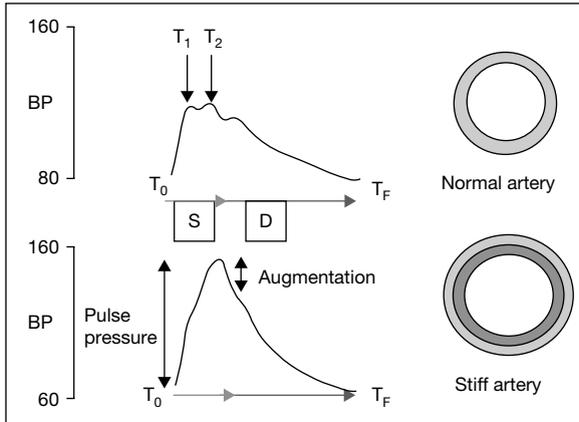
Several parameters of arterial stiffness have been investigated. The shift in importance from diastolic to systolic hypertension has prompted the development of new methods to evaluate arterial compliance. Two of these, derived from the application of applanation tonometry, have emerged as particularly valuable: pulse-wave velocity (PWV) and the augmentation index (AI). Their merits are a simple method of calculation/measurement, reproducible values, and prospectively validated prognostic significance.

PWV is greater in stiffer arteries, and is clearly associated with increased mortality in populations with cardiovascular disease or chronic kidney disease. PWV is assessed through the calculation of the time required for a given pressure waveform to travel from a proximal to a distal site over a known distance. The AI also is clearly associated with survival. AI represents the difference between the first and second systolic peak of the pulse-wave contour divided by PP height. AI is a composite parameter because it expresses the reflective properties of the peripheral distal arterial bed and elastic properties of large arteries. Thus, these 2 measures, although correlated, are not interchangeable or synonymous. PWV and AIx are determined from contour analysis of arterial waveforms recorded by applanation tonometry (SphygmoCortm device, PWV Inc., Westmead, Sydney, Australia) using a highly reproducible technique previously described elsewhere [9, 10]. Briefly, PWV is computed from carotid and radial artery waveforms recorded consecutively (fig. 1), an ECG gated-signal simultaneously recorded, and standard anthropometrical distances ([sternal notch to arterial radial site distance] – [sternal notch to carotid site distance]), as required by the SphygmoCortm software.

PWV and AI assessed by means of applanation tonometry, a simple bedside-applicable technique, may be particularly promising in pharmacological studies dealing with the influence of different substances (mainly antihypertensive drugs) on the viscoelastic properties of large arteries [9–11].

## **Arterial Compliance and Hypertension**

In patients with essential hypertension the arterial compliance is significantly reduced. Also in borderline hypertensives arterial distensibility is already reduced at a young age. It is still unclear whether the reduction of arterial compliance is caused by increased arterial pressure or by reduction of arterial wall dynamic properties.



**Fig. 1.** Typical pulse waveforms from (top) normal and (bottom) stiffened conduit arteries derived from percutaneous tonometry tracings. With reference to a normal artery:  $T_0$  = time of start of cardiac cycle;  $T_F$  = time of finish of cardiac cycle;  $T_1$  = time to outgoing pressure peak;  $T_2$  = time to peak of reflected wave; S = systole; D = diastole. Peaks at  $T_1$  and  $T_2$  coincide in the stiffened artery, leading to augmentation of arterial pressure. AI is the augmentation pressure (the difference between the second and the first systolic peak measured on the aortic pressure waveform) divided by PP (pulse-wave height)  $\times 100$  [11].

Recent studies suggest that intrinsic changes in the arterial wall produce increased stiffness in the arteries. Therefore, the treatment for hypertension must be directed not only to reduce blood pressure but to improve arterial wall compliance [12, 13].

Blood pressure includes a steady component – the mean arterial pressure, and a pulsatile component – the pulse pressure (the difference between systolic and diastolic pressure), which is the result of intermittent ventricular ejection. Pulse pressure is also influenced by the cushioning capacity of large arteries (expressed by compliance) and by the timing and intensity of waves from the heart to vessels and back to the heart (expressed by PWV). All blood vessels have a conduit function that means supplying the organs with blood and a cushioning function that implies dampening the oscillation, but larger arteries are more useful in cushioning and smaller arteries are more useful in blood distribution [14].

The cushioning function is specifically altered during hypertension.

The pathophysiology of arterial rigidity includes structural and functional aspects.

High blood pressure injures the arterial wall, increases matrix collagen deposition and reduces the elastin/collagen ratio. In large arteries 50% of

arterial wall is occupied by the matrix. Therefore, interstitial accumulation of collagen capable of water immobilization has a profound impact on the structure and mechanical properties of the large arteries.

In young people the primary reflected wave returns to the central aorta in diastole, where it augments coronary and cerebral perfusion. If the artery is stiff, the primary reflected wave arrives back at the aortic root during late systole, where it is superimposed on the incident wave, adding to central pulse pressure and cardiac afterload [15]. Arterial stiffness has deleterious effects on left ventricular function and increases myocardial oxygen consumption [16].

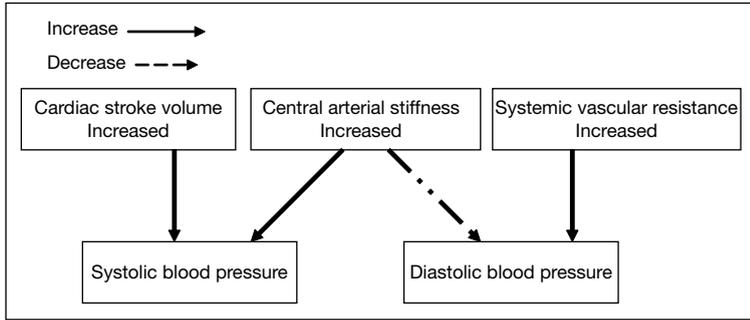
Vascular stiffness is also accompanied by changes in the left ventricle that increase end-systolic chamber stiffness. This does not require renal disease or cardiac hypertrophy to be present. This ventricular arterial stiffening alters the heart response to stress, salt overload or abrupt changes in heart function in patients with heart failure and preserved ejection fraction. The ventricular-arterial stiffness impacts on cardiovascular reserve and blood pressure lability, and also decreases diastolic blood pressure and impairs coronary perfusion [17].

Small arteries also have an important role in hypertension.

Enhanced constriction of these arteries in hypertension may increase peripheral resistance by reducing lumen diameter. According to Poiseuille's law, a small decrease in lumen size may induce significant hemodynamic change and may increase systemic vascular resistance. In small vessels, the main reproducible parameter is media-lumen ratio, measured by histologic techniques, entirely different than large arteries parameters measurement described in the previous section. Studies done on samples taken from gluteal fat confirm that small vessel remodeling does not require true hypertrophy [18]. Here, the media width is increased but the outer and inner diameters are reduced. In early hypertension this eutrophic remodeling is dominant, and only in longstanding hypertension does the well-known hypertrophic remodeling become predominant. This new view of arteriosclerosis-eutrophic remodeling is thought to apply also for large vessels, including the aorta. The 'small aorta syndrome' is more prevalent than dilated aorta in longstanding hypertension [19].

The main role in remodeling is played by the extracellular matrix. Collagen deposition is significantly enhanced in small arteries in patients with essential hypertension. Deposits of collagen contribute to media thickness. Collagen deposition is enhanced by different hormones, such as endothelin-1, angiotensin II and catecholamines. Metalloproteinase activity that degrades extracellular matrix protein is also diminished [20, 21].

Another remodeling process in hypertension is vascular rarefaction. In subjects with severe hypertension the density of arterioles is decreased, which increases vascular resistance [22].



**Fig. 2.** Factors which influence systolic and diastolic blood pressure.

Figure 2 presents, in a concise manner, the factors that influence systolic and diastolic hypertension.

Finally, the change in permeability in the vasa vasorum network, a vascular system that originates from intercostal arteries that provides blood to the arterial wall, may have a role in arterial rigidity by impairing the clearance atherogenic factors and reducing blood wall oxygenation [23].

### **Arterial Compliance and Diabetes**

Diabetic patients show increased arterial stiffness at a relatively young age compared with nondiabetic subjects. Also, diabetes is associated with increased ventricular stiffness in the presence of normal ventricular ejection fraction [24, 25].

Arterial compliance is affected both in insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus subjects from an early stage [26, 27].

This finding suggests that in diabetes the normal aging process of the arterial wall is accelerated. In diabetes, a nonenzymatic reaction between glucose and protein takes place in the arterial wall. At the beginning, glucose and proteins form an unstable and reversible product, called the Schiff base. After a period of time, days to weeks, the unstable product accumulates and forms a more stable product named the Amadori product. The best known Amadori product is hemoglobin A1C, which is glucose linked to the N-terminal valine amino group of the beta chain of hemoglobin.

If exposure to high glucose concentration is longer and hyperglycemia is not lowered, the Amadori product retransforms again into a very stable product, virtually irreversible and resistant to degradation, named ‘advanced glycosylation

end product' or AGE. AGEs alter arterial wall by cross linking throughout the collagen molecule, and the result is loss of compliance. In uncontrolled diabetes, the formation of AGEs is accelerated [24, 28]. Accumulation of AGEs is not an isolated phenomenon and can worsen the damage done by hypercholesterolemia, smoking and renal failure. AGEs increase low-density cholesterol trapping through covalent links. Low-density cholesterol links to collagen and elastin and worsens arterial compliance [29]. Cigarette smoking produces AGEs from tobacco, by an incompletely understood mechanism [30]. Patients with advanced renal failure cannot clear AGEs, and these low-weight molecules accumulate. Modern hemodialysis and peritoneal dialysis methods are unable to remove AGEs efficiently [24].

Recent experimental studies showed that AGE cross-link inhibitors can reverse arterial stiffness and diastolic dysfunction. Extensive presentation of this new class of experimental drugs, AGE cross-link inhibitors, is beyond the scope of this review; for an excellent overview of this issue, see Aronson [24].

The glycation end products affect both large arteries and small arteries. Large artery disease results in stroke and myocardial infarction and small artery disease predisposes to retinopathy and renal failure. Pulse pressure, PWV and AI are strong survival predictors in diabetes, independent of hypertension. Worldwide, diabetic subjects are at substantial cardiovascular risk similar to a nondiabetic subject who has sustained a myocardial infarction. More studies linking PWV to clinical outcomes of diabetes are needed to provide a better understanding of cardiovascular disease in diabetes [31–33].

### **Arterial Compliance, Obesity and Metabolic Syndrome**

Obesity is associated with early vascular changes. Excess body fat, abdominal visceral fat and larger waist circumference have been identified as risk factors for accelerated arterial stiffening in young and older adults. Several pre-existing risk factors, including diabetes, hypertension and dyslipidemia, may particularly increase the negative cardiovascular effects of morbid obesity, causing greater cardiovascular risk earlier in adulthood. There are a number of mechanisms by which increasing adiposity and obesity might contribute to arterial stiffening, both in the short and the long term. First, the state of insulin resistance that commonly accompanies obesity impairs endothelium-dependent vasodilatation and increases the local activity of a variety of growth factors in vascular tissue, promoting collagen production and the development of vascular smooth muscle cell hypertrophy [34, 35].

In addition, the pro-inflammatory state typical of obesity may promote free radical formation, leading to the development of oxidative stress. Elevated

sympathetic nerve activity and norepinephrine-evoked vascular smooth muscle cell contraction may also contribute to obesity-related stiffness [34]. Finally, obesity might increase arterial stiffness through the hormone leptin, which has been shown to promote angiogenesis and vascular smooth muscle cell proliferation [36].

Obesity is often accompanied by a metabolic syndrome, and substantial improvement of the latter also occurs with weight loss. Weight loss in obese individuals leads to rapid improvement of cardiovascular risk factors; however, some studies suggested that weight loss may be hazardous in the long term [37].

A recent study showed that dramatic weight reduction in obese patients with cardiovascular risks corrects metabolic derangements and improves small vessel compliance [34]. Endothelial dysfunction and alterations in function and structure of the arterial wall are detectable earlier in small arterioles than in larger arteries. Lack of change in large artery compliance after weight loss may imply that the process of tissue repair in the large arteries is lengthy and may take several months of stable reduced weight [38].

A metabolic syndrome is defined by the presence of hypertension in association with two or more of the following criteria: high-density lipoprotein <40 mg/dl in men and <50 mg/dl in women, fasting glucose between 100 and 125 mg/dl, triglycerides >150 mg/dl or drug treatment for elevated triglycerides, and waist circumference >102 cm in men or 88 cm in women [39]. Several studies showed that that metabolic syndrome even without diabetes increases the risk of hypertensive target organ damage [40, 41]. Moreover, arterial distensibility is reduced in nondiabetic healthy persons with insulin resistance syndrome and in patients with metabolic syndrome, indicating that arterial stiffness is an early sign of pathology in this disorder [42]. Also, stiffness increases in people with a family history of diabetes [43].

A recent study showed that a metabolic syndrome increases arterial stiffness independent of the effect of hypertension. A possible mechanism is accumulation of advanced glycation end products and enhanced oxidative stress, which alter the structure and function of collagen and elastin.

Insulin resistance, the elevation of leptin and a low level of adiponectin have an additive effect. The elevated pulse pressure in metabolic syndrome can explain the increased risk of cardiovascular morbidity associated with this disease [40].

### **Arterial Stiffness and Survival in Patients with Chronic Kidney Disease**

In industrialized societies, there is a close relationship between hypertension and progressive impairment of renal function. Hypertension and its associated

disorder, diabetes mellitus, are the principal reasons for cardiovascular disease and the initiation of renal replacement therapy with dialysis or transplantation [44]. Cardiovascular events and mortality increase as glomerular filtration rate slows down to below 60 ml/min or albuminuria is present only in a modest degree. In dialysis patients, cardiovascular disease is 10- to 20-fold higher than in the general population, representing at least half of the 15–25% per year mortality rate [45–47]. The fact that only a small minority of people with hypertension develop terminal renal failure is probably best explained by the time interval necessary for renal failure to develop; most hypertensives die of cardiovascular failure before terminal renal failure occurs.

Parameters of arterial stiffness have been associated significantly with cardiovascular morbidity and mortality in patients with essential hypertension and renal failure. Aortic stiffness is an independent predictor of primary coronary events in these patients [49, 50]. Furthermore, increased PWV and AI are strong and independent predictors of cardiovascular death in hypertensive and chronic kidney patients, even without clinically evident atherosclerosis. There is a direct association between parameters of arterial stiffness (PWV and AIx) and the worsening of coronary disease assessed by coronary angiography independent of traditional and nontraditional risk factors: age, dyslipidemia, diabetes, blood pressure, inflammatory status and calcium-phosphate metabolism [51]. Larger values of AI and PWV in terminal renal disease populations are either treated by peritoneal dialysis or hemodialysis, but patients treated by peritoneal dialysis have a worse overall prognosis. This finding is explained by poorer blood volume control and worse lipid profile in patients treated by peritoneal dialysis [52]. There are studies that suggest that in the terminal renal population, the arterial stiffness changes only after renal transplantation, but the data are relatively scarce [53].

There are several potential pathophysiological pathways that could explain why the marked reduction in large artery compliance negatively impacts cardiovascular survival in chronic kidney disease patients. First, increased arterial stiffness is strongly associated, in dialysis patients, with left ventricular hypertrophy and increased left ventricular mass, recognized risk factors for cardiovascular disease. Second, premature return of reflected arterial waves from peripheral sites leads to an elevated pulse pressure and reduces the diastolic period with negative consequences on coronary perfusion, resulting in subendocardial ischemia. Two more processes in chronic kidney disease patients have recently gained considerable attention: these are calcification, and chronic inflammation [49, 50, 54]. Coronary artery calcification has been shown to be very prevalent and extremely advanced, even when compared to nonrenal patients with severe coronary artery disease. There is a strong correlation between coronary artery calcification and aortic PWV in patients with chronic kidney disease. The

second important process relates to systemic inflammation. A strong correlation between C-reactive protein and PWV/AIx was found. All these data demonstrate the role of arterial stiffness in determining the poor outcome of cardiovascular disease in patients with chronic kidney disease [48–50, 54].

### **Arterial Stiffness and Therapy**

Several dietary modifications are efficient in reducing stiffness. Flavonoids are antioxidant substances abundant in fruit, vegetables and dark chocolate that may reduce arterial stiffness [43, 55]. Restriction of dietary sodium and reducing passive and active cigarette and cigar smoking have a beneficial effect on arterial compliance.

Moderate alcohol consumption and regular aerobic exercise (walking, jogging or swimming) may also improve arterial elasticity [43, 56].

Rapid weight loss in patients with morbid obesity and cardiovascular risk factors who underwent laparoscopic adjustable gastric banding was found to be associated with improvement of small artery compliance [34].

The clinical benefits of enhanced external counterpulsation therapy in chronic stable refractory angina patients who fail to respond to conventional therapy, like percutaneous coronary intervention or bypass surgery combined with aggressive antianginal medication, include reductions in angina episodes, nitrate use and improvement in exercise tolerance and quality of life. In a recent study, enhanced external counterpulsation treatment improved AI and PWV [57].

Interventional studies regarding the effect of drugs on arterial compliance are rare. Captopril, propranolol and amlodipine significantly reduced PWV compared with placebo, whereas verapamil had no acute effect on arterial stiffness [58, 59]. Nitroglycerin had a highly significant effect on AI, but just a minor effect on PWV, suggesting that the former parameter may be more useful in pharmacological studies [60]. Spironolactone prevents the accumulation of aortic and myocardial collagen, independent of BP changes, in spontaneously hypertensive rats. Investigations on the long-term effect of spironolactone on arterial stiffness are underway [61]. Counting the multiple effects of the rennin-angiotensin-aldosterone (RAA) axis on the endothelium, RAA inhibition seems particularly attractive in reducing arterial stiffness. Compared with a thiazide diuretic, losartan significantly improved the AI. In patients with essential hypertension, both ACE inhibition and blockade of angiotensin receptor-1 reduced arterial stiffness. Treatment with valsartan in patients with essential hypertension improved arterial compliance of both large and small vessels [62].

This effect was even more pronounced by the ‘dual’ blockade of the RAA system [63, 64].

Clinical studies of hypertensive humans have shown that the antistiffening effect of converting enzyme inhibition is more pronounced in the presence of the c variant of the AT1R receptor gene polymorphism. The hypertensive patients with this type of polymorphism derive more benefit from converting enzyme inhibitors than from treatment with other hypertensive drugs [65].

Omapatrilat, a combined inhibitor of ACE and neutral endopeptidase, has been shown to decrease pulse pressure and proximal aortic stiffness much more than ACE inhibitor alone. This finding indicates the possibility that inhibition of neutral endopeptidase improves aortic elastic characteristics by affecting bradykinin, natriuretic peptides and metalloproteinases [66].

Antihypertensive therapy improves arterial stiffness mainly by reducing BP as a major determinant of diminished arterial compliance. Currently used antihypertensive drugs that may potentially alter arterial stiffness involve the risk of inappropriately decreasing diastolic BP, thus jeopardizing coronary reserve. Moreover, high BP alone definitely does not determine arterial stiffness, which is also influenced by BP-independent structural modifications of the large artery walls [67]. Therapeutic studies focusing on structural improvement in the vessel walls are just beginning. Promising targets in this respect are the matrical proteins. During degenerative processes of the arterial wall, these proteins are establishing nonenzymatic links to glucose (and other similar molecules), and generating advanced glycation end products (AGEs). These AGEs accumulate slowly at the level of low-turnover proteins, such as collagen and elastin, increasing arterial (and myocardial) stiffness. Reducing AGE generation may improve arterial compliance [68]. A recent clinical trial found that a breaker of AGE (ALT-711) improves vascular distensibility and ventricular diastolic distensibility [24, 69]. Treatment with rosiglitazone has reduced hyperinsulinemia and improved small artery elasticity with a tendency to improve large artery elasticity in hypertensive as well as normotensive patients. Rosiglitazone improves insulin receptor sensitivity (IRS), a finding which supports the hypothesis that hyperinsulinemia and IRS participate in the mechanisms of tissue injury and that their improvement induces improvement in arterial elasticity [70]. Therapy with statins may also improve arterial stiffness. Recent investigations showed that PWV improved after fluvastatin and atorvastatin treatment in hypertensive patients, with or without end-stage renal failure [59, 71].

A novel approach to vascular stiffness is treatment with the PDE5a inhibitor sildenafil. Sildenafil is used to treat erectile dysfunction. In the vascular wall sildenafil increases cGMP activation and results in inhibition of fibrosis and vascular relaxation [72].

New drugs that enhance elastin by blocking neutrophil elasticity have been tried, but the study was limited by the toxicity of these drugs [73].

Renal transplantation is the preferred method of renal replacement therapy in most patients with ESRD, because renal transplantation largely restores renal function and patient's quality of life, and considerably improves survival, including CV morbidity and mortality, compared with dialysis patients [74, 75]. AI and PWV in living renal transplant recipients were significantly lower than in HD patients [75–77]. Cyclosporine A treatment, known as a possible factor of renal vasoconstriction, did not induce an acute increase in arterial stiffness by using applanation tonometry [77].

Arterial stiffness seems to have a genetic component, which is largely independent of the influence of blood pressure and other cardiovascular risk factors. Recent studies on animals and humans have looked for the structural and genetic bases of arterial stiffness. They have shown that several genes and molecules are associated with vascular wall stiffening and have illustrated the consequences of changes in these genes and molecules under various clinical conditions. There is strong evidence that arterial stiffness is affected by the amount and density of stiff wall material and the spatial organization of that material. To identify these molecules and their signaling pathways is important for the development of future drug treatments of arterial stiffness [78]. Extensive presentation of the genetic characteristic of arterial stiffness is beyond the scope of this chapter; for an excellent overview, see Laurent et al. [78].

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