Tony Raine Memorial Lecture

Arterial structure and function in end-stage renal disease

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On October 14, 1995, Professor A. Raine (St Bartholomew’s Hospital, London) died at the young age of 46 years. He was a fascinating man who combined a rigorous scientific approach with clinical acumen. He excelled in the fields of hypertension research and nephrological research. He was an inspired investigator whose untimely death is mourned by many colleagues in European nephrology.

NDT commemorates the outstanding contributions of our former subject editor in the field of hypertension by a contribution bearing on the major research topic of the late Professor Raine, i.e. the interrelation of kidney and blood pressure.

Introduction

Epidemiological studies have shown that damage of large conduit arteries is a major contributing factor to morbidity and mortality in patients with chronic kidney disease and in those with end-stage renal disease (ESRD) [1]. Atherosclerosis, a primary intimal disease characterized by the presence of plaques and occlusive lesions, is the most frequent underlying cause of these complications, but many vascular complications arise in uraemic patients in the absence of clinically significant atherosclerotic disease [2,3]. Atherosclerosis represents only one form of structural response to metabolic and haemodynamic alterations which interfere with the ‘natural’ process of ageing [4–6]. The spectrum of arterial alterations in ESRD is broader, including non-occlusive arterial remodeling accompanying the growing haemodynamic burden, and humoral abnormalities associated with chronic uraemia (Fig. 1) [7,8]. The consequences of these alterations are different from those attributed to the presence of atherosclerotic plaques.

Arterial remodeling and arterial function: basic concepts

Arterial remodeling

An arterial wall alters its structure and function in response to direct injury and atherogenic factors or to changes in haemodynamic burden (Fig. 2) [9]. The structural modifications induced by haemodynamic alterations are changes in arterial lumen and/or arterial wall thickness due to activation, proliferation and migration of smooth muscle cells, and rearrangements of cellular elements and extracellular matrix of the vessel wall [9–13].

The mechanical signals for arterial remodeling associated with haemodynamic overload are the cyclic
tensile stress and/or shear stress (Fig. 3) [12–14]. While acute changes in tensile or shear stress induce transient adjustments in vasomotor tone [15,16], chronic alterations of mechanical forces lead to changes in the geometry and composition of the vessel walls that may be considered adaptive responses to long-lasting changes in blood flow and/or pressure [11,17–20].

The characteristics of arterial remodeling depend largely on the nature of haemodynamic stimuli applied to the vessel and on the presence of an intact endothelium [19,20]. Blood pressure is the principal determinant of arterial wall stretch and tensile stress. According to Laplace’s law, tensile stress (σ) is directly proportional to arterial transmural pressure (P) and radius (r), and inversely proportional to arterial wall thickness (h) according to the formula: σ = Pr/h. In response to increased blood pressure or arterial radius, tensile stress is maintained within the physiological range by thickening of the vessel wall with normal internal diameter. Blood flow alterations result in changes in shear stress—the dragging frictional force [21]. Shear stress (τ) is directly proportional to blood flow (Q) and blood viscosity (η) and inversely proportional to the radius (r) of the vessel, according to the formula: τ = Qη/πr³ (Fig. 3). Experimental and clinical data indicate that acute and chronic augmentations of arterial blood flow induce proportional increases in the vessel lumen, whereas decreasing flow reduces arterial inner diameter [10,22,23]. An example of flow-mediated remodeling associates arterial dilation and sustained high blood flow after the creation of an arteriovenous fistula [18]. In this situation, the lumen diameter increases to maintain shear stress within physiological limits. Increased arterial inner diameter is usually accompanied by arterial wall hypertrophy and increased intima-media cross-sectional area (following increases in the radius and wall tension) since changes of shear stress and tensile stress are interrelated because any modification of arterial radius caused by alterations in blood flow and shear stress induces changes in tensile stress.

The process of transforming mechanical forces into remodeling of vascular system implies that there are ‘sensors’ that detect and transmit physical forces to effector cells. Endothelial cells are strategically situated at the blood–vessel wall interface and are the principal candidates for the role of such sensors [24,25]. This mechanosensor activation results in the transduction of physical stimuli into a biochemical signal affecting arterial function through the generation of vasoactive substances [nitric oxide (NO), prostacyclin, endothelins, etc.], the expression of adhesion molecules, the activation and release of metalloproteinases [26–31], and the activation of transforming growth factors [32–35]. The presence of the endothelium is a prerequisite for normal vascular adaptation to chronic changes in blood flow, and experimental data indicate that flow-mediated arterial remodeling can be decreased by inhibiting NO synthase [20,36].

Arterial structure is also altered in response to direct injury and atherogenic factors [37–39]. Atherosclerosis, characterized by the presence of plaques, is primarily an intimal disease, focal and patchy in its distribution, occurring preferentially in medium-sized conduit arteries like epicardial coronary arteries, femoral and iliac arteries, infrarenal aorta, carotid bulb and cerebral arteries, and usually sparing muscular type arteries in the arms, internal mammary and other
Conduit function of arteries. The conduit function is to supply an adequate blood flow to peripheral tissues and organs in accordance with their metabolic needs. Conduit function efficiency is the consequence of the width of the arteries and the very low resistance of large arteries to flow. The conduit function is highly efficient and can accommodate increases in the flow to some tissues, like muscle, by perhaps 10-fold. This physiological adaptability is mediated through acute changes of arterial flow velocity and/or diameter. Diameter changes are dependent on the endothelium, which responds to alterations in shear stress [16,44]. The acute endothelium-dependent vasodilation is limited in several clinical conditions including atherosclerosis [52], hypertension [53], cardiac failure [54], hypercholesterolaemia [55], diabetes [56], menopause [57] and ageing [58]. Under conditions of long-term flow overload, the arterial diameters are enlarged and baseline arterial conductance is increased [10,18]. The principal long-term alterations of conduit function occur through narrowing or occlusion of arteries with restriction of blood flow and resulting ischaemia or infarction of downstream tissues. Atherosclerosis is the most common disease that disturbs conduit function. Owing to the large luminal area of conduit arteries, basal blood flow remains unchanged until the lumen diameter is narrowed by 50%. Beyond 70–80% reduction of the lumen diameter (critical stenosis), basal blood flow is reduced, as is the ability to increase flow during activity [21].

Cushioning (dampening) function of arteries. The role of arteries is also to dampen the pressure and flow oscillations resulting from intermittent ventricular ejection and to transform the pulsatile flow of arteries into the steady flow required in peripheral tissues and organs [21]. During systolic contraction, ~40% of stroke volume is forwarded directly to peripheral tissues, while the remainder is stored in capacitive arteries (mainly aorta and elastic-type arteries). Approximately 10% of the energy produced by the heart is diverted for the distension of arteries and ‘restored’ during diastole to recoil the aorta, squeezing the stored blood forward into the peripheral tissues, thereby ensuring continuous perfusion of organs and tissues. As the energy produced by the heart should serve principally for tissue perfusion, the part of energy used for arterial distension and recoil should be as low as possible. Therefore, the arterial wall must be distensible, i.e. for a given volume change (stroke volume), the developed pressure (pulse pressure) should be as low as possible. The efficiency of the conduit function depends on the viscoelastic properties of arterial walls and the geometry of the arteries, including their diameter and length [21]. The viscoelastic property is best described in terms of stiffness, which expresses the relationship between pressure response (∆P) and change in volume (∆V). Stiffness represents the instantaneous slope of the pressure–volume relationship (S = ∆P/∆V) (Fig. 4). Because the arterial wall is composed of a ‘mixture’ of smooth muscle cells, fibroblasts and connective tissue, containing elastin and collagen fibres, the pressure–volume relationship is non-linear. At a low distending pressure, the tension is borne by elastin fibres, whereas at a high distending pressure, the
tension is predominantly borne by less extensible collagen fibres and the arterial wall becomes stiffer. This arrangement is advantageous because it prevents arterial blood from pooling at high pressure and protects arteries from high pressure-induced rupture. The distribution of elastin and collagen differs between central and peripheral arteries. The collagen:elastin ratio increases from the aorta towards peripheral arteries whose stiffness is higher than that of the central arteries. To facilitate comparisons of viscoelastic properties of structures with different initial dimensions, stiffness can be expressed relative to the initial volume as $\Delta PV/\Delta V$ where $V$ is the initial volume. In contrast to stiffness which provides information about the ‘elasticity’ of the artery as a hollow structure, the elastic incremental modulus ($E_{inc}$) provides direct information on the intrinsic elastic properties of the materials that compose the arterial wall independent of vessel geometry. An increased $E_{inc}$ is characteristic of stiffer biomaterials and is responsible for the leftward shift of the pressure-volume curve (Fig. 4) [21]. The stress applied to arterial segments ($\Delta P$) is the pulse pressure. Owing to the inhomogeneity of the viscoelastic properties of successive arterial segments and the effect of arterial wave reflections (see below), pulse pressure and systolic pressure are amplified from the aorta to the peripheral arteries [59–61]. To determine the elastic properties of arterial segments accurately, the ‘local’ pulse pressure must be measured and taken into consideration. Arterial stiffness can be evaluated by ultrasonography or by the measure of the pulse wave velocity (PWV) over a given arterial segment [8,62]. PWV increases with arterial stiffness [62,63], according to the Moens-Koerteweg formula $\text{PWV}^2 = E_{inc}h/\rho D$, where $E_{inc}$ is incremental modulus, $h$ is wall thickness, $D$ is the artery diameter and $\rho$ is the density. The principal ‘visible’ consequences of arterial stiffening are an increase in systolic pressure and a decrease in diastolic pressure with resulting high pulse pressure [21]. Pulse pressure depends on the interaction between LV ejection (stroke volume) and the physical properties of the arterial system that influence pulse pressure by two mechanisms. First, the direct mechanism involves the generation of a higher pressure wave by the LV ejecting blood into a stiff arterial system, and decreased diastolic recoil resulting in lowered diastolic pressure. Secondly, the indirect mechanism acts via the influence of increased arterial stiffness on PWV and the timing of incident and reflected pressure waves [21,63–67]. Ejection of blood into the aorta generates a pressure wave that is propagated to other arteries throughout the body. This forward-travelling (incident) pressure wave is reflected at any point of structural and functional discontinuity in the arterial tree, thereby generating a reflected (‘echo’) wave travelling backwards towards the ascending aorta. Incident and reflected pressure waves interact constantly and are summed-up in the measured pressure wave. The final amplitude and shape of the measured pressure wave is determined by the phase relationship (the timing) among the component waves [21,60–65]. The timing of incident and reflected pressure waves depends on PWV, the traveling distance of pressure waves, and the duration of LV ejection [65,66]. The shape and amplitude of measured pulse pressure waves depend on the site of pressure recording in the arterial tree [66,67]. Peripheral arteries are close to reflection sites, and the incident and reflected waves in these arteries are in phase and, thus, produce an additive effect. The ascending aorta and central arteries are distant from reflecting sites and, depending on the PWV and arterial length, the return of the reflected wave is variably delayed and thus the incident and reflected waves are not in phase. In young human subjects with distensible arteries and low PWV, the reflected waves affect central arteries during diastole after LV ejection has ceased. This timing is desirable, since the reflected wave causes an increase in ascending aortic pressure during early diastole and not during systole, resulting in aortic systolic and pulse pressures which are lower than in peripheral arteries (only mean blood pressure is almost constant throughout the arterial system) [59–66]. This situation is physiologically advantageous since the increase in early diastolic pressure has a boosting effect on coronary perfusion, without increasing LV afterload. The desirable timing is disrupted by increased PWV due 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 region. The earlier return means that the reflected wave affects the central arteries during systole rather than diastole, thus amplifying aortic and LV pressures during systole and reducing aortic pressure during diastole. In this situation, the pulse and systolic pressure gradients along the arterial tree tend to disappear, resulting in temporal equalization of peripheral and aortic pressures. Increased arterial stiffness is deleterious to LV function. By favouring early wave reflections, arterial stiffening increases peak- and end-systolic pressures.
in the ascending aorta, increasing pressure load and myocardial oxygen consumption and decreasing the diastolic blood pressure as a determinant of coronary perfusion and blood flow distribution. Canine studies have shown that aortic stiffening directly decreases subendocardial blood flow despite an increased mean coronary flow, and that chronic aortic stiffening reduces cardiac transmural perfusion and aggravates subendocardial ischaemia [68]. Furthermore, increased systolic blood pressure induces myocardial hypertrophy (Figs 5–6), and impairs diastolic myocardial function and LV ejection [69,70]. In addition, increased systolic blood pressure and pulse pressure accelerate arterial damage, increasing the fatigue of biomaterials, degenerative changes and arterial stiffening, thereby potentiating the process [39]. Although arterial stiffness is responsible for the acceleration of pressure wave transmission, the intensity of wave reflection is dependent on the reflective properties of the vascular tree (reflectance) that could be altered independently of arterial stiffening. Reflectance depends on the impedance mismatches of successive arterial segments, their branching angles, the vaso-motor tone and geometric properties of microvascular network, and on the body shape responsible for more or less pronounced spatial dispersion of pressure wave [21,39].

The dampening function of the arterial tree is altered primarily during the ageing process and in conditions associated with ‘sclerotic’ remodeling of arterial walls, i.e. associated with increased collagen content and modifications of extracellular matrix (arteriosclerosis) [6,70–73]. Arteriosclerosis is primarily manifest as medial degeneration that is generalized throughout the thoracic aorta and central arteries, causing dilatation, diffuse hypertrophy and stiffening of the arteries [4,5,21,73]. Arteriosclerosis is sometimes considered to be a ‘physiological’ ageing phenomenon, resulting in diffuse fibroelastic intima thickening, increased medial ground substance and collagen, and fragmentation of elastic lamellae with secondary fibrosis and calcification of the media [4–6,71–73]. Age-related arterial alterations leading to stiffening are heterogeneous, being more pronounced in the aorta and central, elastic-type, capacitative arteries than in the peripheral muscular-type limb arteries [62].

Taken together, atherosclerosis is a disorder that typically disturbs conduit function, while arteriosclerosis does not alter it under basal metabolic conditions. However, in Western populations, these two conditions frequently coexist since both progress with ageing and share several common pathogenic mechanisms, which sometimes make the distinction difficult. Atherosclerosis in ESRD patients was the subject of several recent reviews; therefore, in the present article we shall focus on alterations of arterial stiffening in uraemic patients.

**Arterial stiffness, blood pressure and cardiovascular disease in ESRD**

The arterial system of patients with chronic renal failure and ESRD patients undergoes remodeling that is characterized by dilatation and, to a lesser degree, arterial intima-media hypertrophy of central, elastic-type, capacitative arteries, and isolated wall hypertrophy of peripheral muscular-type conduit arteries [7,8,74–76]. In ESRD patients, this remodeling is associated with arterial stiffening due to alterations of the intrinsic properties of arterial wall materials ($E_{inc}$) including those arteries free of atherosclerosis, such as upper arm arteries [7,8,77–80].

Large arteries, like the aorta or common carotid artery, are enlarged in ESRD patients in comparison with age-, sex- and pressure-matched control subjects. Arterial enlargement is already observed at the onset of dialysis, suggesting that arterial remodeling takes place early in the course of renal failure. The internal dimensions of large arteries are influenced by many factors. Several factors, for example age, sex or mean blood pressure, are non-specific for ESRD patients, while others, such as high blood flow velocity and systemic blood flow rate, are more specific for this patient population (Fig. 7) [8]. In ESRD patients, chronic volume/flow overload (anaemia, arteriovenous shunts,
sodium and water retention) creates conditions for arterial remodeling [8]. The intima-media thickness of elastic-type arteries is proportional to changes in diameter, with similar wall-to-lumen ratio, while muscular-type arteries are characterized by wall hypertrophy and increased wall-to-lumen ratio [8,75]. This heterogeneity is related to a predominance of flow-related remodeling in central arteries under conditions of combined pressure and flow overload [81]. According to Laplace’s law, arterial wall hypertrophy could be considered a response to increased tensile stress, and when blood pressure increases, regardless of the internal radius, the wall-to-lumen ratio should increase in order to normalize tensile stress [21]. This increase was observed in non-uraemic populations but not in ESRD patients whose wall-to-lumen ratio in large conduit arteries was not related to pressure changes [80]. The difference between the observed relationships suggests that conduit arteries could have limited capacity to hypertrophy in response to a combined flow and pressure load. This possibility was documented by Savage et al. [82] and Konings et al. [83], who showed that their ESRD patients had no arterial wall thickening. The altered hypertrophic response could be due to qualitative alterations of biomaterials present in ‘uraemic vasculopathy’. Arterial distensibility is ‘pressure-dependent’ [21] and, in essential hypertensive patients, the decreased arterial distensibility is due to higher distending blood pressure rather than to arterial wall thickening and modifications in intrinsic biomaterial stiffness [84,85]. When adjusted for differences in blood pressure (i.e. under isobaric conditions), the arterial distensibility and/or elastic modulus of essential hypertensive subjects are more distensible (in muscular conduit arteries) or similar (in elastic capacitive arteries) compared with those observed in normotensive control subjects [84,85]. This concept is different from the observation made in ESRD patients, in whom common carotid artery stiffness is increased in comparison to age- and blood pressure-matched non-uraemic subjects [8,75].

In ESRD patients, arterial hypertrophy is accompanied by alterations in the intrinsic elastic properties of the vessel wall (increased $E_{\text{tot}}$) that contribute to creating and amplifying the pressure load. This modification affects elastic and muscular-type arteries, including arteries free of atherosclerosis like the radial artery [75]. The observation that the incremental modulus of elasticity is increased in ESRD patients strongly favours altered intrinsic elastic properties or major architectural abnormalities like those seen in experimental uraemia and the arteries of uraemic patients, namely fibroelastic intimal thickening, increased extracellular matrix and high calcium content with extensive medial calcifications [86–88].

Finally, the presence of generalized endothelial dysfunction in uraemic patients probably also contributes substantially to arterial alterations in ESRD patients. As shown experimentally by Lévy and colleagues [89,90], the endothelium influences the mechanical and geometric properties of large arteries, and removing the endothelium causes an increase in arterial diameter. In ESRD patients, large artery alterations are associated with decreased post-ischaemic arterial vasodilatation and decreased flow-debt repayment, suggesting a relationship between arterial modifications and endothelial dysfunction [91–96].

An association between arterial remodeling and functional alterations with lipid abnormalities is not obvious and was found only irregularly. London et al. [77] and Saito et al. [78] reported an inverse relationship between aortic PWV and HDL cholesterol. Burdick et al. [97] and Nishizawa et al. [98] described a positive relationship between carotid intima-media thickness and IDL or LDL cholesterol. The most frequently observed factors associated with arterial stiffening in ESRD seem to be alterations in calcium and phosphate metabolism. Experimental studies suggest that some of the effects of renal failure on arterial remodeling and increased fibrogenesis depend on the permissive action of parathyroid hormone [99]. In chronic haemodialysis patients, aortic PWV was found to be associated with medial calcinosis of conduit arteries and increased calcium phosphate product [77,78]. Kawagishi and colleagues [74] reported that a high phosphorus level was associated with carotid artery intima-media thickening, while increased serum PTH was a risk factor for increased wall thickness of femoral arteries. Studying renal transplant recipients, Barenbrock and co-workers [100] observed an association between high PTH levels and decreased common carotid artery distensibility. Recent data indicate that medial calcification and extensive calcifications of the arterial tree are the dominant factor accounting for the increased arterial stiffening [101].

**Consequences of arterial stiffening in ESRD patients**

**Pathophysiological consequences.** The pathophysiological consequences of arterial stiffening and wave reflections are those already described, i.e. increased...
ventricular afterload associated with ventricular hypertrophy, decreased subendocardial perfusion and increased mechanical fatigue of arteries.

The clinical consequences. Arterial stiffening is associated with changes in blood pressure profile, characterized by isolated increase in systolic pressure and/or increased pulse pressure. Increased pulse pressure can result from increased systolic pressure as well as from decrease diastolic pressure which is typical for advanced arteriosclerosis and is responsible for the diastolic pressure stabilization or decline observed after the age of 60 [102]. In the general population, the pulse pressure is an independent cardiovascular risk factor, observed principally in older subjects >50 years old [102–105]. The reason is that systolic pressure as well as pulse pressure result from the interaction between cardiac factors (stroke volume, ejection velocity) and the opposition to LV ejection. Pulse pressure can also increase due to increased stroke volume (as observed for example in trained athletes with spontaneous bradycardia and high stroke volume and is not associated with higher risk). The risk associated with high pulse pressure is observed when the increase in pulse pressure is associated with arterial stiffening. Recent epidemiological studies have shown that pulse pressure is associated with risk of death in patients undergoing haemodialysis [106,107]. In early renal disease patients, Levin et al. [108] have shown that increased systolic blood pressure is an independent predictor of left ventricular hypertrophy and its progression over time (odds ratio of 1.11 for each 5-mm Hg increase).

Increased arterial stiffness of elastic type arteries is associated with reduced creatinine clearance and observed already in subjects with mild-to-moderate impairment of renal function [109], and in patients with chronic renal failure [83]. In ESRD patients, LVH is closely related to systolic or pulse pressure [8,66,77]. Arterial stiffness and early wave reflection are the principal determinants of systolic and pulse pressures in ESRD patients and are associated with LVH [77] and its progression over time [110].

While in the past, the consequences of arterial stiffness for patient outcome have not been directly evaluated, a recent study demonstrated that arterial stiffening and increased wave reflections are per se independent predictors of all-cause and cardiovascular death in ESRD patients as well as in the general population. Blacher and colleagues [111] applied logistic regression and Cox analyses to various parameters of a cohort of 241 subjects with ESRD and showed aortic PWV to be an independent and significant predictor of all-cause and cardiovascular mortality. After adjustment for all risk factors (age, pre-existing cardiovascular disease, blood pressure, anaemia, LV hypertrophy, etc.), the odds ratio for PWV (>1227 cm/s) was 4.4 [confidence interval (CI): 2.3–8.5] for all-cause mortality and 5 (CI: 2.3–10.9) for cardiovascular mortality (Fig. 8). Similar results were observed by Shoji et al. [112] in diabetic patients with ESRD. In that study it was demonstrated that the influence of arterial stiffening on mortality outweighed the role of diabetes. Finally, Laurent et al. [113] showed that aortic PWV was an independent predictor of all-cause and cardiovascular mortality in the general population. PWV is a complex parameter integrating arterial geometry and intrinsic elastic properties as described by the Moens–Korteweg equation (see above). Based on Cox analyses, Blacher and colleagues [114] showed that the principal factor associated with PWV as a predictor of cardiovascular and all-cause mortality in ESRD was increased elastic modulus. The latter modulus is associated with extensive arterial calcifications which are also a strong predictor of mortality in ESRD patients [115]. As already mentioned, increased vascular reflectance influences wave reflections independently of arterial stiffness. In ESRD patients, more marked effects of wave reflections are associated with cardiovascular and all-cause mortality independently and in parallel with arterial stiffening [116].
Therapeutic interventions on arterial stiffness and their impact on patient outcome.

Epidemiological studies have shown that left ventricular hypertrophy and arterial stiffening are tightly associated and that both are independent cardiovascular risk factors. An improvement of arterial stiffening should be one of the major objectives in the prevention and treatment of cardiovascular complications in ESRD. Dialysis by itself does not increase arterial distensibility [117], and some studies indicate that arterial function worsens with time on dialysis [101,118,119].

We know from studies in essential hypertensive, non-uraemic subjects that long-term antihypertensive therapy induces reverse arterial remodeling with improvement of the arterial viscoelastic properties [120]. During recent years, a few controlled studies were aimed at examining the effect of antihypertensive drugs on the function of large arteries in ESRD patients on intermittent haemodialysis therapy. It has been shown that long-term treatment with antihypertensive drugs effectively lowered blood pressure, and significantly decreased aortic PWV and wave reflections [121–123]. The antihypertensive drugs decreased aortic PWV to a large extent in response to blood pressure lowering as such. This blood pressure dependency of arterial stiffness offers the possibility to investigate whether the regression of arterial stiffness has a favourable effect on long-term patient outcome. This possibility was studied in a follow-up study by Guérin et al. [124] in 150 haemodialysis patients whose blood pressure was decreased by association of ‘dry weight’ adjustment and antihypertensive drugs. The results showed that, in patients whose PWV decreased in parallel with blood pressure, the survival was much better than in those ESRD patients whose PWV was insensitive to blood pressure decrease (Figs 9 and 10). The blood pressure sensitivity of arterial stiffening offers the possibility to investigate whether the regression of arterial stiffness has a favourable effect on long-term patient outcome. This possibility was studied in a follow-up study by Guérin et al. [124] in 150 haemodialysis patients whose blood pressure was decreased by association of ‘dry weight’ adjustment and antihypertensive drugs. The results showed that, in patients whose PWV decreased in parallel with blood pressure, the survival was much better than in those ESRD patients whose PWV was insensitive to blood pressure decrease (Figs 9 and 10). The blood pressure sensitivity of arterial stiffening was also associated with a decrease in left ventricular hypertrophy, which by itself favourably influenced survival in ESRD patients [125]. The effects of stiffness attenuation and regression of left ventricular hypertrophy were independent of blood pressure changes as such. The same study showed that the prescription of the ACE inhibitor perindopril was associated, independently of changes in PWV or blood pressure, with a decreased relative risk of cardiovascular mortality of 0.19 (95% CI: 0.14–0.43).

As already mentioned, extensive calcifications of the arterial tree are associated with increased stiffness, non-response to antihypertensive agents and increased risk of death [101,115]. Vascular calcifications are the consequence of an active ‘osteogenic’ process in the vessel wall and are associated with several factors including hyperphosphataemia and possibly a positive calcium balance (frequently associated with adynamic bone disease owing to oversuppression of hyperparathyroidism) [101,126,127]. Recent studies have challenged the current practice of controlling hyperphosphataemia with calcium-containing binders, and have shown that there is a significant association between arterial calcification score and the amount of calcium ingested [101,126]. These associations should be confirmed. Of note, a recent study using the non-calcium-containing compound sevelamer has shown that the administration of this compound, but not that of calcium binders, can prevent the progression of arterial calcifications in dialysis patients, as detected by electron beam computed tomography [128].

Conclusions

The vascular complications in ESRD are ascribed to two different, although associated mechanisms, namely atherosclerosis and arteriosclerosis. Arteriosclerosis is characterized by diffuse dilation and hypertrophy of large conduit arteries and stiffening of arterial walls and represents one clinical form of an accelerated ageing process. These alterations are associated with several haemodynamic changes characteristic of ESRD, such as flow/volume overload and increased circumferential tensile stress due to increased arterial diameters and/or intra-arterial pressure. As a result of these
arterial changes, the systolic pressure is abnormally increased in ESRD patients, while the diastolic pressure is usually within the normal range or even lower. The main adverse effects of arterial stiffening are: (i) an elevated LV afterload with development of LV hypertrophy and increased myocardial oxygen demand; and (ii) altered coronary perfusion and blood flow distribution with relative subendocardial ischemia. Epidemiological studies have demonstrated the impact of arterial abnormalities on cardiovascular disease evolution and identified arterial remodeling and stiffening as independent predictors of overall and cardiac mortality in ESRD patients.

References


110. Matsumoto Y, Hamada M, Hiwada K. Aortic stiffness is closely related to the progression of left ventricular hypertrophy in patients receiving hemodialysis. Angiology 2000; 51: 933–941


