# Vascular and cardiac remodeling in end-stage renal disease

**G. M. London, S. J. Marchais, A. P. Guerin, F. Metivier and B. Pannier**
Manhes Hospital (France).

Cardiovascular complications are the principal cause of morbidity and mortality in end-stage renal disease patients[1]. Myocardial infarction and cerebrovascular events related to occlusive lesions at the site of atheromatous plaques are the most frequent underlying cause[2]. The frequency of these complications led to the hypothesis of the existence of an accelerated atherosclerosis in end-stage renal disease, and research has concentrated on metabolic factors of vascular remodeling associated with atheromatous plaques. Nevertheless, atherosclerosis represents only one form of large conduit arteries remodeling. The spectrum of arterial remodeling in end-stage renal disease is much wider, including structural changes related to hemodynamic alterations whose functional consequences are different from those related to the presence of plaques.

## CONCEPT OF VASCULAR REMODELING

Vascular remodeling is an adaptative process occuring in response to long-lasting changes in arterial pressure and/or flow, and whose ultimate effect tends to maintain the constancy of tensile and/or shear stresses[3]. According to Laplace's law the tensile stress ($\sigma$) is directly proportional to arterial transmural pressure (P) and radius (r), and inversely proportional to arterial wall thickness (h) according to the formula: $\sigma = Pr/h$. In response to increased blood pressure the arterial wall hypertrophies principally by thickening of the media. Luminal diameter is reduced or unchanged, leading to decrease of the ratio of the width of the lumen to the width of the wall which tends to normalise the tensile stress. (This pressure-induced rearrangement in distal resistive arteries and arterioles where the luminal diameter is reduced but medial layer is not hypertrophied-"eutrophic remodeling"[4]). Another form of large conduit arteries remodeling involves primarily changes in shear stress inducing changes in luminal diameter with secondary adaptation in wall thickness[5, 6]. Shear stress ($\tau$) is directly proportional to blood flow (Q) and blood viscosity ($\mu$) and inversely proportional to the radius (r) of the vessel, according to the formula: $\tau = 4.Q.\mu/\pi.r^3$. Increase in shear stress could be the consequence of increased blood viscosity, decreased arterial diameter, or increased blood flow and blood flow gradient applied on endothelial surface. The most classical example of flow mediated remodeling include arterial dilation associated with sustained high blood flow after creation of arteriovenous fistula[7]. In this condition, the luminal diameter increases to maintain a constant shear stress. Endothelium plays a prominent role in the process of vascular remodeling being strategically located at the interface between blood stream and the vessel wall[3]. The exact mechanisms mediating the mechanotransduction and response of endothelium to hemodynamic stimuli are not completely elucidated. Alterations in tension activate stretch-sensitive cationic channels promoting generation of mitogenic and trophic factors[8-12]. Changes in shear stress activate flow-sensitive potassium channels and hyperpolarisation of smooth muscle cells, as well as generation of nitric oxide and vasodilating prostacyclin[13-18]. Endothelial mechanisms are involved not only in acute changes in vascular tone and diameter, but play also a role in chronic increase in blood flow[19, 20].

## ARTERIAL REMODELING AND ARTERIAL FUNCTION: BASIC PRINCIPLES

The arterial remodeling is associated with changes in the function of arterial tree, which are different from those related to presence of atherosclero-

Correspondence address:
Dr. G. London.
8. Grande Rue.
Fleury-Merogis.
91712 Ste. Geneviève des Bois.
France.

tic plaques. Indeed, the arterial system has two distinct, interrelated functions: 1) to deliver an adequate supply of blood to body tissues - the *conduit function;* 2) to smooth out the pulsations occuring with intermittent ventricular ejection - the *cushioning function*[21, 22].

### Conduit function of arteries

The efficiency of conduit function in related to the width of the arteries and the almost constancy of mean blood pressure along the arterial tree, the mean pressure drop between the ascending aorta and the arteries in the forearm or leg being 2 to 3 mmHg in supine position[23, 24]. Alterations of conduit function occur through narrowing or occlusion of arteries with restriction of blood flow and resulting ischemia or infarction of tissues downstream[24].

Atherosclerosis characterised by the presence of plaques is the most common disease that disturbs conduit function[24]. Atherosclerosis is primarily an intimal disease, focal and patchy in its distribution, occuring preferentially in the coronaries, femoral arteries, carotid bifurcation and infrarenal aorta[24]. Focal compensatory enlargement occurs at discrete sites of narrowing immediately adjacent to more or less normal areas[8, 25]. Mechanisms of atherogenesis-related arterial remodeling are complex, including the action of many humoral factors and also mechanical factors such as tensible stress and shear stress[8, 25-28]. The role of mechanical factors is confirmed by the high prevalence of atherosclerosis in hypertension, with a predilection of atherosclerotic plaques for certains sites characterised by disturbances of flow pattern and shear stress, like orifices, bifurcations, bending or pronounced tapering[8, 29].

Atherosclerosis is a frequent cause of morbidity in patients with end-stage renal disease and myocardial infarction or cerebrovascular events occupy an important place in the mortality of these patients. This has been shown in pioneer study by Lindner et al[2] and has been extensively confirmed by numerous subsequent reports.

### Cushioning function of arteries

The principal role of arteries as cushions is to dampen the pressure oscillations resulting from intermittent ventricular ejection («Windkessel» effect)[21, 22, 24]. Indeed, large arteries can instantaneously accomodate the volume of blood ejected from the heart, storing part of the stroke volume during systolic ejection and draining this volume during diastole, thereby ensuring a continuous perfusion of organs and tissues[21, 22]. The efficiency of windkessel function is due to the viscoelastic properties of arterial walls and the «geometric» characteristic of the arteries including their diameter and length[21, 22]. The principal alteration in cushioning function is due to the stiffening of arterial walls. The consequences of wall stiffening are an increased systolic and pulse pressure and a decrease in diastolic pressure[21, 22]. Hence the viscoelastic properties of the arterial system influence the level of systolic as well as diastolic pressure. Through promoting an increase in mean-, peak-, and end-SBP in the ascending aorta arterial stiffening is responsible for an increase in myocardial oxygen consumption, while the decrease in mean DBP tends to impair the coronary blood supply[30-32]. Furthermore, increased SBP induces myocardial hypertrophy, impairs diastolic myocardial function and ventricular ejection[33, 34]. In addition increased SBP and pulse pressure accelerates arterial damage, increasing the fatigue, degenerative changes and arterial stiffening feeding a vicious circle[24].

Cushioning function is altered primarily during aging process[21, 24, 35-38] and in conditions associated with «sclerotic» remodeling of arterial walls, i.e. associated with increased collagen contain and changes in extracellular matrix (arteriosclerosis). Arteriosclerosis is primarily a medial degenerative condition that is generalized thoughout the thoracic aorta and central arteries, causing dilatation, diffuse hypertrophy and stiffening of arteries[24]. Arteriosclerosis is sometimes considered as a «physiological» aging phenomenon which is accelerated by hypertension[39-41]. Arteriosclerosis results in diffuse fibroelastic intima thickening, an increase in medial group substance and collagen, and fragmentation of elastic lamellae with secondary fibrosis and calcification of the media. These changes are more pronounced in the aorta and central arteries than in the limb arteries[38].

## ARTERIAL REMODELING IN END-STAGE RENAL DISEASE (ATHEROSCLEROSIS EXCLUDED)

The arterial system is ESRD patients undergoes structural remodeling very similar to changes with aging, and is characterized by diffuse dilation, hypertrophy and stiffening of the aorta and major arteries (table I)[32]. Although part of the arterial alterations in ESRD patients are associated with the aging proccess, several features of arterial remodeling observed in chronic uremia are different from those of the natural aging process[32].

**Table I.** Arterial structure and function.

| Parameters | Controls | ESRD |
|---|---|---|
| CCA pulse pressure (mmHg) | 48.0 ± 17.0 | 58.3 ± 21.0** |
| Subendocardial viability index (%) | 173 ± 30 | 157 ± 31** |
| $Ao_{bif}$ diameter (mm) | 15.0 ± 1.8 | 17.0 ± 2.6*** |
| CCA diameter (mm) | 5.55 ± 0.65 | 6.25 ± 0.87*** |
| CCA intima-media thickness (μm) | 678 ± 105 | 777 ± 115*** |
| CCA wall/lumen (ratio) | 0.24 ± 0.03 | 0.25 ± 0.03 |
| CCA intima-media croos-sectional area ($mm^2$) | 13.4 ± 3.3 | 17.5 ± 4.5*** |
| CCA distensibility ($KPa^{-1}.10^{-3}$) | 24.0 ± 12.7 | 17.8 ± 8.8** |
| CCA compliance ($m^2.KPa^{-1}.10^{-7}$) | 6.00 ± 2.50 | 5.15 ± 2.00* |
| CCA elastic incremental modulus ($KPa.10^3$) | 0.46 ± 0.23 | 0.61 ± 0.35** |
| Carotid-femoral PWV (cm/s) | 957 ± 180 | 1055 ± 290* |

Abbreviations are: CCA, common carotid artery; $Ao_{bif}$, aorta at bifurcation level; PWV, pulse wave velocity.
* P < 0.05; ** P < 0.01; *** P < 0.001.

## Hemodynamic factors of arterial remodeling in chronic uremia

*Arterial changes associated with alterations in flow.* In ESRD patients, conditions such as anemia, arteriovenous shunts and overhydration induce a state of chronic volume/flow overload associated with increased systemic and regional blood flow and flow velocity, creating conditions for systemic arterial remodeling[32, 42]. This has been illustrated by cross sectional studies which showed a direct relationship between the diameter of the aorta and of major arteries and blood flow velocity (figure 1)[32], as well as by studies indicating that arterial enlargement could be limited by adequate fluid removal during dialysis[43]. Therefore it appears that the systemic arterial enlargement observed in ESRD results in part from chronic volume and flow overload, and from this point of view differs from changes observed during normal aging. Chronic volume and flow overload are also responsible for the increased internal dimensions of the left ventricle[42]. The common influence of flow overload on arterial and ventricular dimensions induces a dimensional coupling between the heart and the conduit vessels[32] (figure 2).

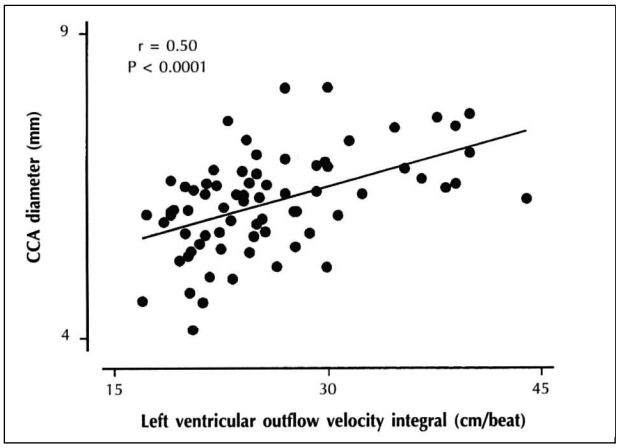


*Fig. 1.—Scatterplot showing the correlation between common carotid artery (CCA) diameter and left ventricular outflow velocity integral in ESRD patients.*

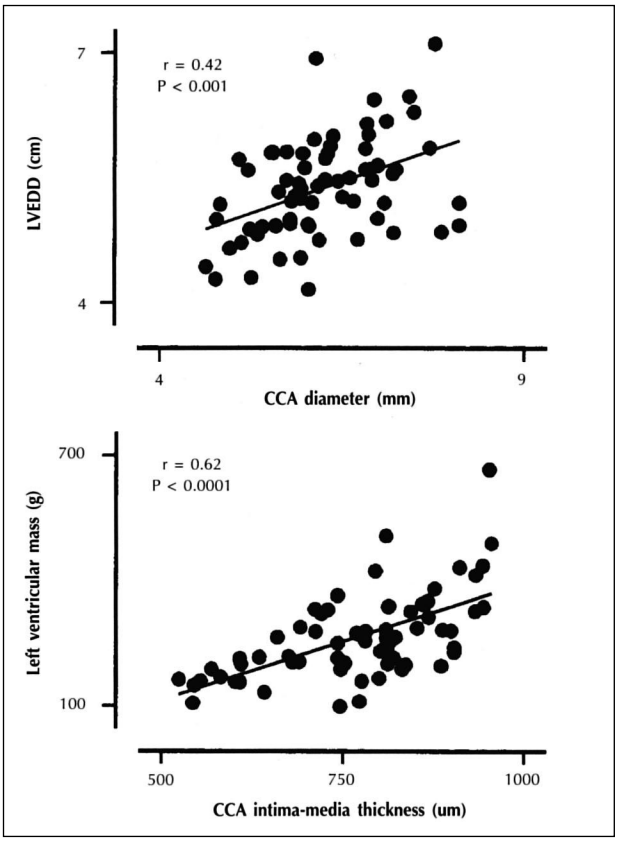


*Fig. 2.—(Above panel) Scatterplot showing the correlations between common carotid artery (CCA) diameter and left ventricular diastolic diameter (LVEDD) and (below panel) between CCA intima-media thickness and left ventricular mass in ESRD patients.*

*Arterial changes associated with increase in tensile stress.* In comparison with non-uremic patients, the intima-media thickness of major central arteries is increased in ESRD patients[32, 44]. Like in general the population, in ESRD patients arterial wall thickness increases with age, distending pressure, and arterial diameter[32]. The increase in wall thickness is proportional to changes in diameter, and this is a logical consequence of Laplace's law, whereby wall tension is directly proportional to arterial radius. Nevertheless, according to the same law, when the

blood pressure increases, and whatever the internal radius, the wall-to lumen ratio should increase in order to normalize the tensile stress. This is observed in nonuremic populations[45, 46] but not in ESRD patients[32]. Conduit arteries have probably a limited capacity to respond adequately to a combined flow and pressure stimuli. This was observed in ESRD patients on radial artery supplying arteriovenous fistula, and also in experimental conditions[7, 47]. Indeed, in vein grafts subjected to separate mechanical factors such as circumferential stretching and changes in blood velocity, Dobrin et al[47] demonstrated that changes in flow influence intimal thickening, whereas medial thickening responds to changes in wall stress. Intimal thickening occurs in response to low flow velocity, whereas medial thickening occurs in response to increased parietal tension. Therefore in ESRD patients increased tensile stress could induce medial hypertrophy, while increased flow would decreased the intimal thickness. As the present ultrasonographic devices are unable to differentiate intima from media this remains purely speculative.

In ESRD, the increase in arterial intima-media thickness is associated with decreased arterial distensibility (figure 3). In ESRD patients decreased arterial distensibility results directly from arterial wall hypertrophy, and incremental modulus of elasticity in increased in comparison with age and pressure matched non-uremic controls[34-37, 48]. The different relationship between hypertrophy and intrinsic elastic properties in nonuremic subjects and ESRD points to qualitative differences in the «hypertrophic process», being in favor of altered intrinsic elastic properties as observed in experimental uremia and in vitro in arteries of uremic patients, namely fibroelastic intimal thickening, calcification of elastic lamellae and ground substance deposition[49, 50].

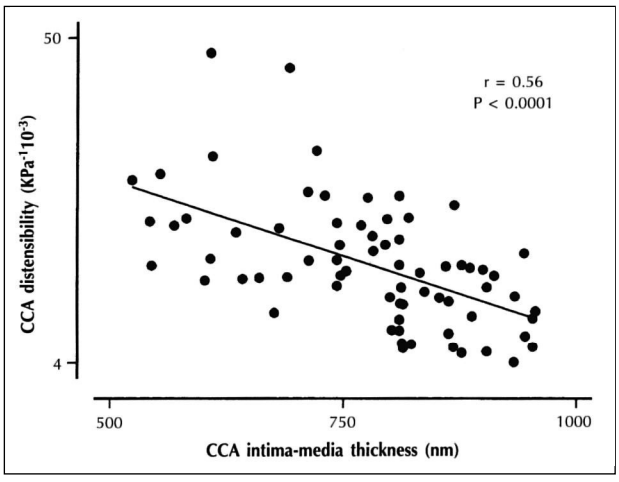


*Fig. 3.—Scatterplot showing the correlation between common carotid artery (CCA) intima-media thickness and CCA distensibility in ESRD patients.*

## CONSEQUENCES OF ARTERIAL STIFFENING IN ESRD PATIENTS

The most important consequence of arteriosclerosis is arterial stiffening resulting in an increased left ventricular systolic stress and an abnormal relationship between systolic and diastolic tension-time integrals[21, 22, 31, 32]. The principal consequences of these alterations are left ventricular hypertrophy (figure 2) and altered coronary perfusion with decrease in subendocardial flow (figure 4)[32, 34].

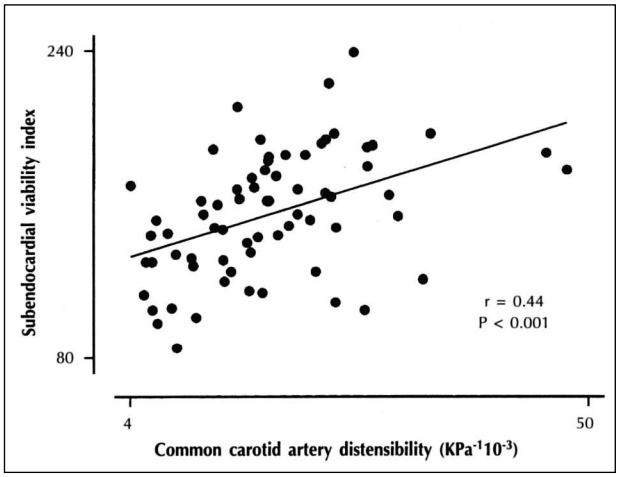


*Fig. 4.—Scatterplot showing the correlation between the CCA distensibility and subendocardial viability index in ESRD patients.*

The important factors relating the pressure load to LV hypertrophy and altered LV function are the peak and end-systolic pressures in the aorta and central arteries, which are critically dependent on the physical properties of arteries[21, 22, 24]. Previous studies have shown that LV hypertrophy in ESRD was correlated to increased pulsatile pressure load due to increased arterial stiffness and wave reflections[32, 34]. Among ESRD patients, significant relations existed between comparable cardiac and vascular parameters[32]. LV diameter and arterial diameters are correlated and significant correlations were observed between the common carotid artery intima-media thickness and intima-media cross-sectional area and LV wall thickness and/or LV mass (figure 2). These relationships are independent of other factors like age, body surface area, gender[32]. Moreover, independently from the blood pressure level, the extend of left ventricular hypertrophy is

directly proportional to decrease in aortic distensibility. However, in ESRD patients a significant correlation was observed between arterial diameter and LV wall thickness suggesting also the existence of a direct link between arterial dilation and LV hypertrophy[32]. Indeed, the inertial effects are greater in enlarged arteries since larger blood-filled arteries require the heart to produce excess work in order to accelerate blood against larger inertial forces during ejection.

The second most important consequence of arterial stiffening is compromised coronary perfusion[31, 32]. Canine studies have shown that aortic stiffening directly decreased subendocardial blood flow despite an increase in mean coronary flow, and that chronic aortic stiffening reduced cardiac transmural perfusion and aggravated subendocardial ischemia[21, 22, 31, 51] (figure 4). Cardiac ischemia and alterations in subendocardial perfusion are frequently observed in uremic patients despite patent coronary arteries[52, 53]. This has been recently shown in ESRD patients in which the changes in large artery structure and function were associated with decreased diastolic/systolic tension-time integral (subendocardial viability index) (figure 4), an index of the propensity for myocardial ischemia when there are altered hemodynamic forces in the absence of occlusive arterial lesions[32]. Besides the role of abnormal structure and function of aorta and major arteries this alterations are partly related to structural abnormalities of intramyocardial microvasculature. In uremic rats, Amann et al[50] have shown diminished myocardial capillary density and thickening of intramyocardial arterioles due to smooth muscle cells hyperplasia.

## CONCLUSIONS

Arterial remodeling in patients with ESRD includes dilation and intima-media hypertrophy of large conduit arteries. This remodeling is principally related to chronic flow overload and increased tensile stress. The consequences of arterial remodeling are an increased ventricular afterload and development of left ventricular hypertrophy and compromised subendocardial perfusion.

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