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Vascular disease and atherosclerosis in uremia

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SUMMARY

Epidemiological and clinical studies have shown that cardiovascular disease in patients with end-stage renal disease (ESRD) is frequently related to damage of large conduit arteries. Arterial disease is responsible for the high incidence of ischemic heart disease, peripheral artery diseases, left ventricular hypertrophy and congestive heart failure. The vascular complications in ESRD are due to two different but associated mechanisms, namely atherosclerosis and arteriosclerosis. Whereas the former principally affects the conduit function with ischemic lesions being the most characteristic consequence, the latter primarily disturbs the cushioning function of large arteries. Arteriosclerosis in ESRD patients is characterized by diffuse dilation and hypertrophy of large conduit arteries and stiffening of arterial walls, and represents a clinical form of an accelerated aging process. The main clinical characteristics of arterial stiffening are changes in blood pressure with isolated increase in systolic pressure and normal or lower diastolic pressure. The consequences of these alterations are: i) an increased LV afterload with development of LV hypertrophy and increased myocardial oxygen demand, and ii) altered coronary perfusion and subendocardial blood flow distribution. Epidemiological studies have identified arterial remodeling and stiffening as independent predictors of overall and cardiac mortality in ESRD patients.

Key words: ***End stage renal disease. Cardiovascular disease.***

ENFERMEDAD VASCULAR Y ATEROSCLEROSIS EN LA UREMIA

RESUMEN

Estudios clínicos y epidemiológicos han demostrado que la enfermedad cardiovascular en los pacientes con enfermedad renal crónica terminal (ERCT) está relacionada con lesiones de los grandes vasos. La enfermedad arterial es responsable de cardiopatía isquémica, arteriopatía crónica periférica, hipertrofia ventricular izquierda e insuficiencia cardíaca congestiva. Las complicaciones vasculares de la ECRT son secundarias a dos mecanismos distintos pero asociados; se trata de la ateroesclerosis y de la arterioesclerosis. El primer mecanismo afecta la conducción del flujo sanguíneo siendo las lesiones isquémicas las principales consecuencias, el segundo altera la función amortiguadora del pulso por las arterias de gran tamaño. La arterioesclerosis en la ERCT se caracteriza por la dilatación difusa y la hipertrofia de arterias de gran tamaño así como por la rigidez arterial y representa

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una forma clínica de envejecimiento acelerado. La característica clínica principal de los cambios de la rigidez arterial son los cambios de presión arterial con una presión arterial sistólica aislada y una presión arterial diastólica normal o baja. Las consecuencias de estas alteraciones son las siguientes: i) aumento de la postcarga del ventrículo izquierdo (VI) y hipertrofia del VI y aumento del consumo de oxígeno, y ii) alteración de la perfusión coronaria y de la distribución del flujo sanguíneo. Estudios epidemiológicos han identificado el remodelado arterial y la rigidez como factores predictores de la mortalidad global y cardiáca en la ERCT.

Palabras clave: ***Insuficiencia renal crónica terminal. Enfermedad cardio-vascular.***

INTRODUCTION

Cardiovascular disease is a major cause of morbidity and mortality in patients with end-stage renal disease (ESRD)[1]. While the most frequent underlying cause of these complications is atherosclerosis characterized by the presence of plaques and occlusive lesions[2-5], the spectrum of arterial alterations includes structural changes whose alterations concern principally the viscoelastic properties of large arteries.

ARTERIAL FUNCTIONS

The arteries have two distinct, interrelated functions: 1) to deliver an adequate supply of blood to peripheral tissues —the *conduit function,* and 2) to smooth out pressure oscillations due to intermittent ventricular ejection —the *cushioning function*[6].

Conduit Function

The conduit function, i.e., the capacity to transfer blood from the left ventricle to peripheral organs (arterial conductance), is related to the width of the arteries and the almost constancy of mean blood pressure along the arterial tree. This function is efficient, since in conditions of increased demand the blood flow can increase 5 to 8 times over the baseline value. Alterations in conduit function can be functional (endothelium-dependent vasodilatation is limited in hypertension, cardiac failure, hypercholesterolemia, smoking) or due to structural remodeling. The principal alterations of conduit function occur through narrowing or occlusion of arteries with restriction of blood flow and resulting ischemia or infarction of tissues downstream. Atherosclerosis characterised by the presence of plaques is the most common disease that disturbs conduit function. Atherosclerosis is primarily an intimal disease, focal and patchy in its distribution. Mechanisms of atherogenesis are complex, including lipid disturbances, thrombogenesis, production of vasoactive substances and growth factors and mediators of inflammation. Atherogenesis depends also on mechanical factors such as alterations in shear stress, with predilection of plaques for sites characterised by disturbances of flow pattern and shear stress, like orifices, bifurcations, bending and pronounced arterial tapering.

Dampening function of Arteries

The second role of arteries is to dampen the and flow pressure oscillations resulting from intermittent ventricular ejection. Arteries can accommodate the volume of blood ejected from the heart, storing part of the volume during systole and draining this volume during diastole, thereby ensuring continuous perfusion of organs and tissues. The efficiency of dampening function depends on viscoelastic properties of arterial walls (expressed in term of compliance, distensibility, or incremental elastic modulus) and their «geometric» characteristics including their diameter and length[6].

The principal alteration in cushioning function is due to the stiffening of arterial walls (i.e. decrease in compliance or distensibility, or increase in elastic modulus), with increase in systolic and pulse pressure as the principal consequences[7]. Two mechanisms are involved. The first involves the generation of a higher pressure wave by the left ventricle ejecting into a stiff arterial system, and a higher velocity (PWV —pulse wave velocity increases with the stiffening) at which is the pressure wave propagated forward (incident wave) to other arteries[6-8]. The second mechanism is *indirect* via the influence of increased arterial stiffness and PWV on the timing of incident and reflected pressure waves[8]. Indeed, the incident wave is reflected at any points of structural and func-

tional discontinuity of the arterial tree, generating a reflected wave traveling backward towards ascending aorta. Incident and reflected pressure waves interact and are summed up in a measured pressure wave. The amplitude of the measured pressure wave is determined by the timing between the component waves. The desirable timing is disrupted by increased PWV due to arterial stiffening and increased PWV responsible for an early return of reflected wave from the periphery to the aorta. The earlier return means that the reflected wave impacts on the central arteries during systole rather than diastole, amplifying aortic and ventricular pressures during systole and reducing aortic pressure during diastole. An increase of arterial stiffness is disadvantageous to left ventricular function, inducing left ventricular hypertrophy, increased myocardial oxygen consumption and impairs diastolic myocardial function and ventricular ejection. Increased systolic and pulse pressures accelerate arterial damage, increasing the degenerative changes and arterial stiffening feeding a vicious circle[9-12]. Arterial stiffening is altered primarily during aging process and in conditions associated with increased collagen content (arteriosclerosis), diffuse fibroelastic intima thickening, fibrosis and calcification, and is generalized throughout the thoracic aorta and central arteries, causing dilatation, and diffuse hypertrophy.

ARTERIAL REMODELING AND FUNCTION IN ESRD

The arterial alterations in ESRD are heterogeneous and associates atherosclerosis (development of plaques) and remodeling assosiated with ageing (arteriosclerosis) and hemodynamic alterations. Atherosclerosis and arterial occlusive lesions are the most frequent causes of cardiovascular morbidity in patients on renal replacement. Occlusive lesions principally involve the medium-sized conduit arteries, and coronary insufficiency, peripheral artery disease, and cerebrovascular events occupy an important place in the mortality of these patients. The high incidence of atherosclerosis-related complications led Lindner, et al.[2] to hypothesize that atherogenesis is accelerated in chronic hemodialysis patients. However, it remains a matter of debate whether or not the atherogenesis of dialysis patients is accelerated and whether or not the nature of atherosclerotic plaques is similar in hemodialysis patients and the general population. Ultrasonographic studies have shown a much higher prevalence of calcified plaques in ESRD patients than in age-matched controls in whom soft plaques are more frequent[5]. While ESRD produces atherogenic factors essentially unique to uremia, including dyslipidemia, calcium-phosphate alterations, malnutrition and activation of cytokines and inflammatory mediators. Arteriosclerosis, is typically observed in conditions of arterial mediacalcosis. Atherosclerosis and arteriosclerosis are frequently comorbid, and in ESRD patients the extent of calcifications and the degree of arterial stiffening are independent predictors of mortality. The pathophysiology of calcifications are complex with hyperphosphatemia-associated treatments (aluminum and calcium phosphate binders) and PTH oversuppression (parathyroidectomy) playing a significant role. Metal-free, calcium-free phosphate binders such as sevelamer can reduce coronary and aorta calcification scores. Recent studies have shown that the excessive use of calcium phosphate binders could favor the presence of plaque calcification[13]. The factors specific for ESRD are additive to the number of risk factors observed in subjects with preserved renal function, such as age, hypertension, smoking, diabetes, male gender, and insulin resistance. Many hemodialysis patients already have significant vascular lesions before initiating dialysis and, in many patients, especially older patients, the generalized atherosclerosis can be the primary cause of renal failure. Hypertension is a frequent complication in ESRD, and an association between high BP and occlusive arterial lesions was found in chronic hemodialysis patients.

Arterial system in patients with ESRD undergoes structural remodeling which is in many aspects similar to ageing and are characterized by dilation, hypertrophy, and stiffening of the aorta and major arteries[14,15]. Although large part of the arterial alterations are associated with alterations in hemodynamic factors, non-hemodynamic factors more or less specific to ESRD could play an important role. Chronic increase in blood flow induces dilation of arterial luminal area and wall hypertrophy[15-17]. 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. 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, as well as by studies indicating that arterial enlargement could be limited by adequate fluid removal during dialysis[14]. Even in the absence of blood pressure changes, the increase in arterial radius is responsible for augmentation of tensile stress (Laplace's law) that induces activation of hypertrophic process.

In comparison with blood pressure and age-matched non-uremic patients, the intima-media thickness of major central arteries is increased in ESRD patients[15, 18]. The increased intima-media thickness is associated with decreased arterial distensibility, increased PWV, and early return of wave reflections[15, 19, 20]. In essential hypertensive patients, decreased arterial distensibility is primarily due to higher distending blood pressure rather than to arterial wall thickening and structural modifications[21]. In ESRD patients arterial distensibility is decreased in comparison to age- and blood pressure-matched non-uremic population, and is proportional to arterial wall hypertrophy. In ESRD patients arterial hypertrophy is accompanied by alterations of the intrinsic elastic properties of arterial walls (increased *Einc*). This modification affects elastic and muscular type arteries, including arteries free of atherosclerosis, like the radial artery[22]. The observation that the incremental modulus of elasticity was increased in ESRD patients more strongly favors altered intrinsic elastic properties or major architectural abnormalities like those seen in experimental uremia and the arteries of uremic patients. The nature of these qualitative changes remains to be precisely determined, but several alterations, namely fibroelastic intimal thickening, calcification of elastic lamellae and ground substance deposition are classically observed in these patients[23, 24]. The factors associated with these alterations are not precisely identified, but endothelin[25], parathyroid hormone[26] and chronic inflammatory conditions seem to play an important role.

CONSEQUENCES OF ARTERIAL REMODELING

Arterial stiffening results are increased systolic and pulse pressures, and due to early wave reflections abnormal increase in aortic and left ventricular systolic pressure. The principal consequence of these alterations is left ventricular hypertrophy[4, 7, 15, 27]. Among ESRD patients, significant relations existed between comparable cardiac and vascular parameters[15] 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. The second important consequence of arterial stiffness is compromised coronary perfusion. Cardiac ischemia and alterations in subendocardial perfusion are frequently observed in uremic patients despite patent coronary arteries[28].

In the past, the clinical consequences of arterial stiffening on cardiovascular structure and function have been poorly evaluated. Blacher, et al.[28] applied logistic regression and Cox analyse to the characteristics of a cohort of 241 subjects with ESRD and were able to identify increased aortic PWV as a significant independent predictor of cardiovascular and all-cause mortality. PWV is a complex parameter integrating arterial geometry and intrinsic elastic properties described by Moens-Korteweg equation $PWV^2 = Eh/2r$, where E is the elastic modulus (*Einc*), r is the radius, h is the wall thickness. Blacher, et al[29] have shown that the principal factors associated with the aortic PWV as a predictor of cardiovascular and all-cause mortality in ESRD were the elastic modulus and dilatation of arteries.

CONCLUSIONS

The principal pathophysiological consequence of vascular alterations in ESRD is decreased arterial distensibility and increased PWV with early wave reflections whose principal clinical consequences are: increased systolic and pulse pressures, LV hypertrophy and altered coronary circulation. In the absence of controlled studies, it is difficult to propose therapeutical interventions aimed to prevent or treat arterial abnormalities. It is only during recent years that a small number of controlled studies have been conducted which were aimed at examining the effect of antihypertensive drugs on the function of large arteries. It has been shown that long-term administration of either calcium channel blocker nitrendipine, or the ACE inhibitor perindopril led to a decrease in pulse wave velocity and arterial wave reflections, indicative of an improvement of vessel wall elasticity. Nevertheless, these studies did not conclude whether the improvement of elastic properties were due only to decrease in blood pressure or to alterations in intrinsic properties of arterial walls.

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