Hipertensive heart disease in the patient with chronic kidney disease

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INTRODUCTION

Chronic renal disease (CRD) represents a public health problem for several reasons, among which its relationship with other epidemic and chronic diseases with a poor prognosis, such as cardiovascular disease (CVD),[1] stands out. Indeed, CRD promotes the development of cardiovascular disease (CVD), especially in those patients presenting high blood pressure and/or diabetes mellitus.[2] On the other hand, CRD promotes CVD morbimortality at the expense of increasing the atherosclerotic ischemic events and heart failure.[3]

Hypertensive heart disease is a good example for analyzing the relationship between CRD and CVD. Although the main defining criterion is the presence of left ventricular hypertrophy (LVH) in the absence of another cause different from high blood pressure,[4] diastolic dysfunction is the functional hallmark of hypertensive heart disease.[5] The severity of diastolic dysfunction correlates with that of LVH, so that 30%-45% of hypertensive patients with chronic heart failure present severe LVH, ultrasonographic signs of diastolic dysfunction and preserved ejection fraction.[6] In fact, hypertensive heart disease represents the leading cause of heart failure with preserved ejection fraction or diastolic heart failure.[7]

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Given that CRD may facilitate the development of hypertensive heart disease and that the latter may condition the renal patient's prognosis, this review will consider some general issues on the pathophysiology and clinical expression, with a especial attention on the particular way how CRD influences on the development and progression of this heart disease.

MYOCARDIAL STRUCTURAL REMODELING IN HYPERTENSION

A series of changes in the histological composition of the myocardium take place in hypertensive heart disease, which constitute the basis of its structural remodeling.[8] Remodeling includes multiple changes in cellular (cardiomyocytes and not cardiomyocytes) and no-cellular elements (extracellular matrix, intra-myocardial vessels) (table I and fig. 1). Among these changes, cardiomyocytes hypertrophy, fibrosis of the interstitium and the perivascular region, and alterations in the wall of intra-myocardial arteries and arterioles stand out. Whereas the first and third ones represent the adapting response of the parenchymal and vascular muscle cells to pressure overload in an attempt to normalize the systolic stress of the ventricular and arterial wall, respectively, the second one is related to the changes in collagen myocardial metabolism, which are not related as much to hemodynamic overload as to the action of several humoral factors.

From a histological perspective, myocardial fibrosis is the consequence of an excessive accumulation of collagen fibers, mainly type I fibers (fig. 2).[9] This accumulation is the result of an increased collagen synthesis by fibroblasts and myofibroblasts that is not compensated by a similar increase in collagen degradation by matrix metalloproteinases. Two types of evidences suggest that hypertensive myocardial fi-

Table I. Histological changes in the myocardium determining its structural remodeling in hypertensive heart disease[8]

Cellular changes
- Cardiomyocytes hypertrophy.
- Decreased number of cardiomyocytes (due to excessive apoptosis).
- Fibroblasts hyperplasia (due to excessive proliferation).
- Increased number of myofibroblasts (due to fibroblasts transformation).
- Hypertrophy and hyperplasia of the muscle cells of the intramyocardial vessels.
- Infiltration by monocytes, macrophages, and master cells.

Non-cellular changes
- Excessive extracellular deposition of collagen fibers.
- Excessive extracellular deposition of fibronectin.
- Thickening of the intramyocardial arteries and arterioles wall.
- Decreased number of capillaries.

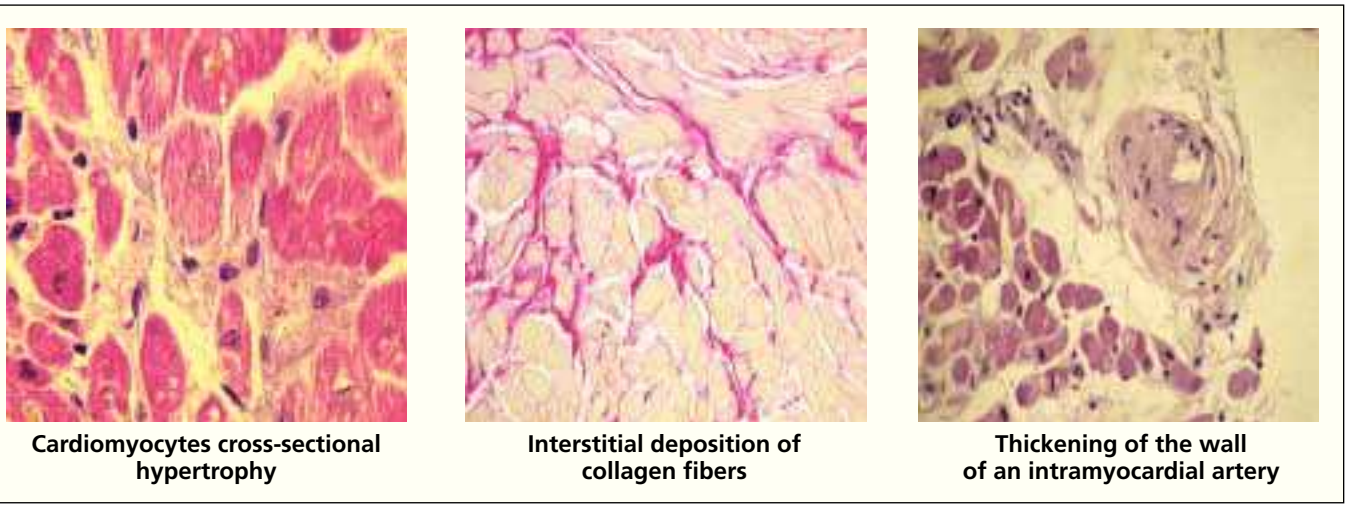

Figure 1. Microscopic images of the myocardium from a patient with hypertensive heart disease showing the three main lesions in myocardium remodeling. The two lateral panels correspond to hematoxylin-eosin staining and the central panel to a picrosirius red staining (the collagen fibers are stained in the red).

brosis develops in response to non-hemodynamic factors.[8] In the first place, fibrosis occurs not only within the left ventricle but also in the right ventricle, the interventricular septum, and the left atrium in hypertensive patients. In the second place, it has been shown that the capacity of antihypertensive therapy to reduce fibrosis in hypertensive patients is independent of its antihypertensive efficacy. Thus, hypertensive myocardial fibrosis may be considered as a consequence of a lost balance between pro-fibrotic and anti-fibrotic factors existing in the myocardium, favoring the former (table II). Together with hypertension, other factors linked to the genetic substratum, demographics and lifestyle, as well as the coexistence of diseases such as obesity or diabetes mellitus also contribute to this unbalance.

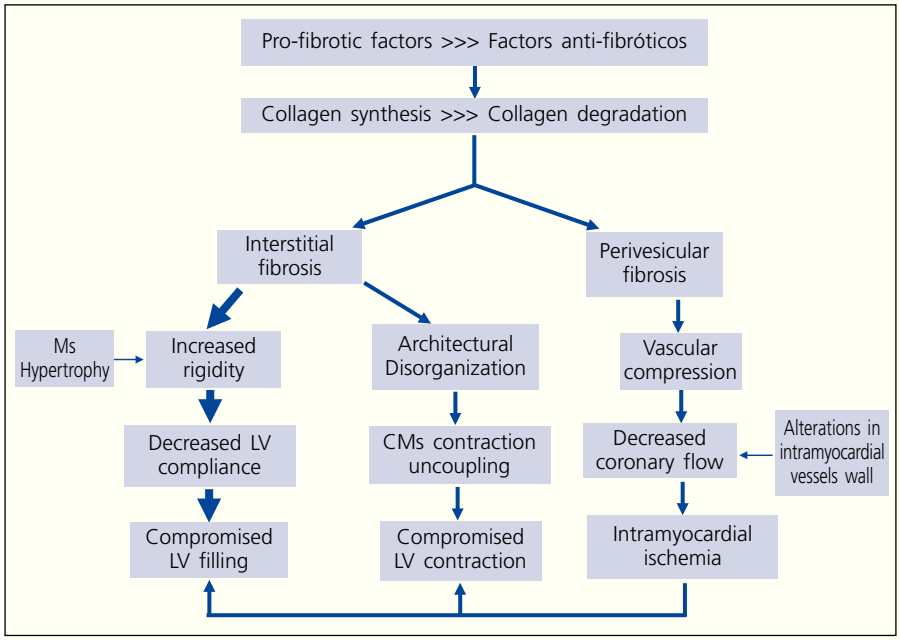

Figure 2. Pathways connecting myocardial fibrosis, and other components of structural remodeling, with heart dysfunction in arterial hypertension. The arrows thickness is related with the importance of the contribution of each component to diastolic dysfunction/failure. (CMs, cardiomyocytes; LV, left ventricle).

IMPACT OF MYOCARDIUM REMODELING ON DIASTOLIC FUNCTION

Although myocardium remodeling alters the global function of the left ventricle and perfusion and electric activity of the myocardium (fig. 2), its main harmful effect is that it affects diastolic function. During diastole there is an early rapid filling phase related to active relaxation of the cardiomyocytes and a passive late phase that depends on the elastic properties of the left ventricle. Thus, diastolic dysfunction is characterized by alterations in the left ventricle relaxation and/or compliance. The myocardium remodeling adversely affects both diastole phases (fig. 2).

Impact cardiomyocytes hypertrophy

Cardiomyocytes hypertrophy may affect both phases of the diastolic function. It has been described that hypertrophic cardiomyocytes have reduced relaxation velocity due to decreased cytosolic calcium (Ca^{2+}) transport to the sarcoplasmic reticulum because of a reduced activity of the Ca^{2+} or Ca^{2+}-ATPase pump.[10] On the other, an overexpression of the titin N2B isoform, at the expense of the expression of the N2BA isoform, has been described in hypertrophic cardiomyocytes from patients with diastolic heart failure.[11] Titin is a protein from the cardiomyocyte cytoskeleton linking the Z

lines with the core of the large filament and determining the resting rigidity of the cardiomyocytes.[12] Given that the N2B isoform of the titin is more rigid than the N2BA isoform, it excess may contribute to diastolic function deterioration by reducing the compliance of the ventricular chamber.

Impact of the alterations of intramyocardial vessels

A decrease in the coronary flow reserve has been described in hypertensive patients, although it is not directly related with LVH since it has also been observed without heart hypertrophy.[13] Among the vascular mechanisms accounting for this impairment we may highlight the presence of intramyocardial arteries lesions that thicken the vascular wall and decrease the lumen, as well as the alterations in arterioles reactivity leading to excessive vasoconstriction.[14] Sasaki *et al.*[15] described an association between the compromise in the coronary reserve and impairment in diastolic relaxation in hypertensive patients. Since cardiomyocytes relaxation is a Ca^{2+}-ATPase-mediated process, and thus energy-dependent, it is reasonable to think that ischemia secondary to lower coronary reserve will compromise diastolic function through this mechanism.

Impact myocardial fibrosis

Myocardial fibrosis is the most important structural determinant factor for the increase in myocardial stiffness and the subsequent decrease in ventricular compliance[16] (fig. 2). In fact, by using the Young's elastic module method, it has been verified that intrinsic stiffness of type I collagen fibers is 30 fold higher than cardiomyocytes rigidity. In this sense, the association of fibrosis to diastolic dysfunction in hypertension has been evidenced in several experimental and clinical studies. In spontaneously hypertensive rats (SHR) with LVH, Brilla *et al.*[17] showed a decrease in left ventricle compliance during diastole that was corrected when the rats were administered low doses of lysinopril, an angiotensin converting enzyme inhibitor (ACEI), which cleared myocardial fibrosis without modifying the blood pressure or LVH. The same group corroborated the previous findings in old SHR with LVH and heart failure and higher compromise of ventricular compliance, by showing that fibrosis reduction with lysinopril was associated with an improvement in the mechanical properties of the ventricle and in heart function, independently of arterial blood pressure and ventricular mass.[18] In hypertensive patients, Sugihara *et al.*[19] and Müller-Brunotte *et al.*[20] described a negative association between diastolic function and the amount of myocardial fibrosis already present in patients without LVH, which

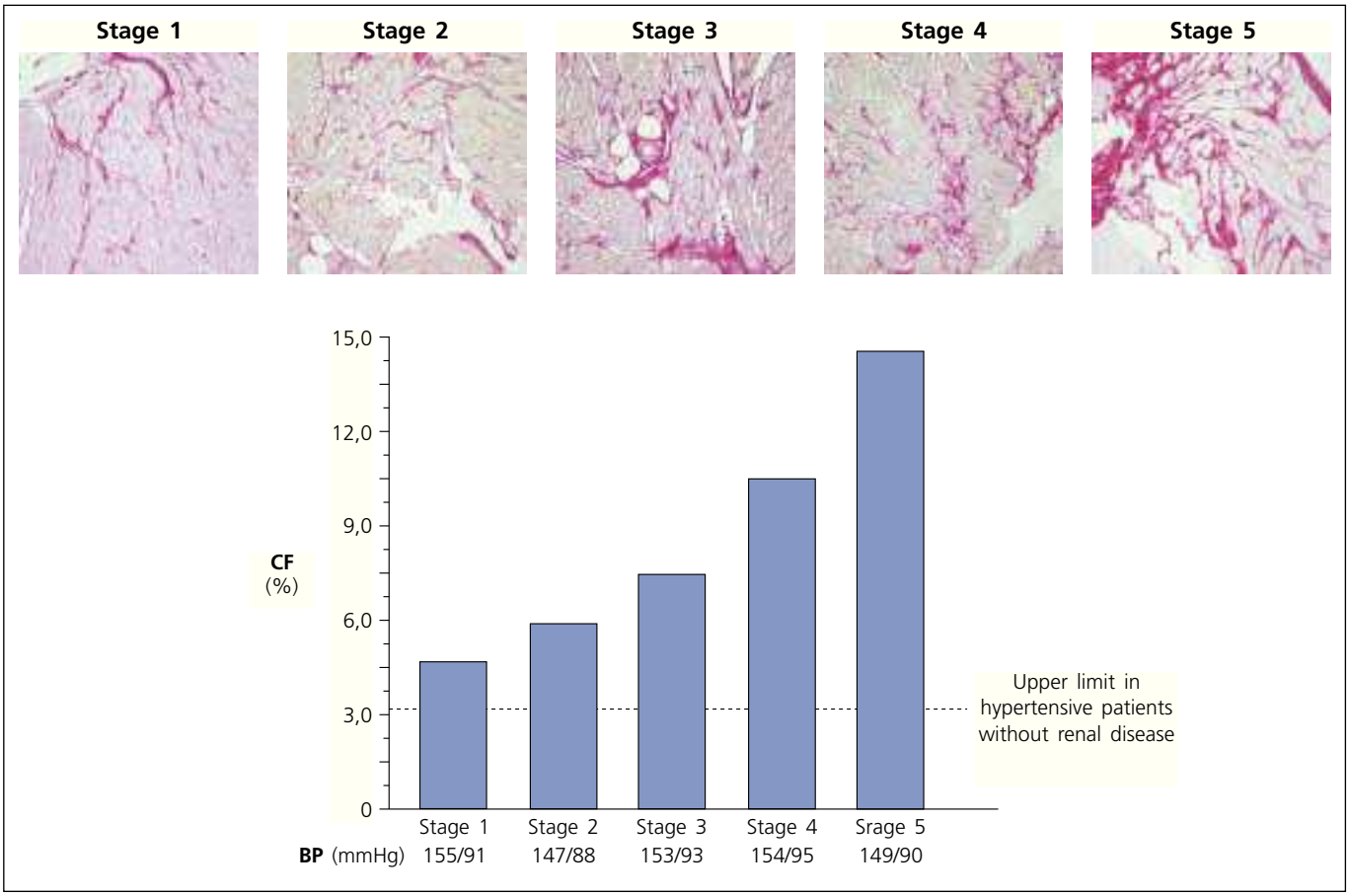

Figure 3. Microscopic images of the myocardium from five patients with hypertensive heart disease at the different stages of chronic renal disease (top panels). Histograms with the proportion of myocardium volume occupied by collagen fibers (CF) in each one of these patients and arterial blood pressure values (BP) present at the time of the histopathological study (bottom panels). The histological preparations are stained with picrosirius red (the collagen fibers are stained in red). (Elaborated with data from the author's registry, JD).

was strengthen when there was LVH. Brilla *et al.*[21] showed in hypertensive patients with LVH that a decrease in the amount of fibrosis after lysinopril therapy was accompanied by an improvement in diastolic function, independently of regression of LVH. On the other hand, our group observed that in hypertensive patients with LVH treated with an angiotensin II AT_1-receptor antagonist there was an association between fibrosis reduction and the decrease in the rigidity of the left ventricle chamber independently of the reduction of blood pressure or left ventricle mass.[22]

In more advanced and severe cases with hypertensive heart disease there is a great and chaotic accumulation of fibers with the subsequent changes in their especial orientation, which interferes with cardiomyocytes stretching preceding their contractile shortening, as well as with the synergistic contraction of the cardiomyocytes bundles and the resulting ejection strength transmission to the ventricular chamber, all these factors compromising systolic function.[16] Thus, in old SHR with heart failure, an association between the presence of severe fibrosis and the development of diastolic function has been observed.[18] In addition, in hypertensive patients with long-lived hypertensive heart disease and heart failure, an association between the presence of severe fibrosis and depression of the ejection fraction has also been observed.[23,24]

HYPERTENSIVE HEART DISEASE IN CRD PATIENTS

Having reviewed the general aspects of hypertensive heart disease, it is convenient to consider some aspects acquiring a particular character in the setting of CRD.

Factors facilitating myocardium remodeling in CRD

The three lesions constitutive of the myocardium structural remodeling are a constant finding in heart biopsies and necropsy studies of patients with CRD and hypertension.[25,26] Even more, the severity of the lesions, for instance fibrosis, increases with the stage of CRD (fig. 3). Many experimental evidences support the notion that a series of biochemical and hormonal factors promoting the development and severity of the lesions of myocardium remodeling are encountered in the progression of CRD (table III). The clinical evidence available suggests that some of these factors start to operate already from the initial stages and others act preferentially in more advanced stages of CRD. Among the former we may consider oxidative stress resulting from an excessive production of the superoxide anion,[27] an excess of cytokines such as b-transforming growth factor[28] and cardiotrophin-1,[29] and a systemic inflammatory status.[30] Among the latter, we may point out anemia,[31,32] hyperphosphatemia, the excess of parathormone and vitamin D deficiency,[33,34] hyperactivity of the sympathetic nervous system,[35] excessive activation of the renin-angiotensin-aldosterone system,[36,37] the excess of advanced glycation end-products,[38] endogenous ouabain[39] and asymmetric dimethyl-arginine,[40] free tri-iodo-thyronine[41] and carnitine deficiency,[42] and accumulation of filterable products toxic for the myocardium.[43] We may say that it is likely that synergistic events may occur between the factors mentioned leading to redundant mechanisms of myocardial damage. For instance, initial stimulation in myocardial production of cardiotrophin-1 in response to the mechanical overload imposed by hypertension to the myocardium[44] may further increase in response to anemia-related myocardial hypoxia,[45] as well as the direct influence on the cardiac cells of the excess of angiotensin II[46] and norepinephrine[47].

Finally, it is necessary to bear in mind that the proteasome activity is impaired in advanced stages of CRD, which translates in an excessive or insufficient degradation of the skeletal muscle proteins.[48] One of the proteins which degradation depends on the proteasome is titin,[49] so that lower activity of the proteasome would lead to titin accumulation within the cardiomyocytes and an increase in cardiomyocytes stiffness and deterioration of diastolic ventricular filling.

Clinical characteristics of hypertensive heart disease in CRD

High blood pressure is the main factor associated to left ventricle growth and dysfunction in CRD patients from the early stages of CRD, and this association is maintained independently of other factors at all stages of CRD.[50] Besides, the prevalence of concentric LVH[51,52] and of diastolic dysfunction[53,54] is higher among hypertensive patients with CRD than in hypertensive patients without CRD, and it increases as CRD progresses. Patients with CRD and hypertensive heart disease have an increase risk for the development of chronic diastolic heart failure, which manifests as severe intolerance to physical exertion, and it may even lead

Table II. Factors implicated in myocardial fibrosis[9]

Direct pro-fibrotic factors (stimulators of collagen synthesis over its degradation):
- Vasoconstrictive substances (e.g., angiotensin II).
- Hormones (e.g., aldosterone).
- Cytokines (e.g., TGF-β).
- Other molecules (ligands of RAPP-gamma, free radicals, etc.).

Directs anti-fibrotic factors (stimulators of the collagen degradation over its synthesis):
- Vasodilating substances (e.g., bradykinin).
- Hormones (e.g., cortisol).
- Cytokines (e.g., TNF-alpha).
- Other (ligands of RAPP-alpha, etc.).

Indirec pro-fibrotic factors (favoring the predominance of pro-fibrotic factors over anti-fibrotic ones):
- Genetic factors (e.g., polymorphism I/D of the ACE gene).
- Sex-linked factors (e.g., male gender).
- Dietary factors (e.g., salt overload).
- Associated diseases (e.g., diabetes, obesity, chronic renal disease).
- Mechanical factor (e.g., pressure overload).

TGF-β, transforming growth factor-beta; RAPP, receptor-activated peroxisome proliferators; TNF-α, tumor necrosis factor-alpha; ACE, angiotensin-converting enzyme.

Table III. Effects of factors facilitating myocardium remodeling in chronic renal disease on the structural remodeling components

	Cardiomyocytes hypertrophy	Myocardium fibrosis	Alterations of the intramyocardial vessels
Oxidative stress	X	X	X
Excess of TGF-β		X	(X)
Excess of cardiotrophin-1	X	(X)	
Inflammation		X	
Anemia	X	(X)	
Hyperphosphatemia		X	
Excess of parathormone	X	X	
Vitamin D deficit	X	X	
Sympathetic hyperactivity	X		X
SRAA activation	X	X	X
Excess of AGEs		X	
Excess of endogenous ouabain	X		
Excess of ADMA			X
T3 deficit	X		
Carnitine deficit	X		
Excess of myocaridal toxins	X	(X)	

TGF-β, transforming growth factor-beta; RAAS, renin-angiotensin-aldosterone system; AGEs, advanced glycation end-products; ADMA, asymmetric di-methyl-arginine; T3, tri-iodo-tironine. X, evidenced facilitating effect; (X) controversial facilitating effect.

to acute pulmonary edema or sudden intra-dialysis hypotension in dialyzed patients.[53] In patients with CRD, the mortality from diastolic heart failure is higher than that from systolic heart failure with decreased ejection fraction.[55] In addition to being associated to diastolic heart failure, in patients with CRD hypertensive heart disease is associated with an increase risk for aortic valve dysfunction, ventricular arrhythmias, atrial fibrillation, and worsening of a coexistent coronary heart disease.[56,57]

Diagnosis of hypertensive heart disease in CRD

The observations from the preceding section indicate that hypertensive heart disease in CRD patients constitutes a relevant condition from the clinical and prognostic perspective, so that special attention must be paid to identify and managing it. In this setting, normal and tissular Doppler echocardiography becomes essential to morphologically and functionally characterize the left ventricle and also to stratify the patients according to their risk for presenting future complications (for instance, the greater the left ventricle mass the higher the likelihood of developing diastolic heart failure will be, and the higher the dimensions of the left atrium, the higher the risk for presenting atrial fibrillation).[58] Echocardiography with integrated backscatter, a technique assessing the tissular composition by analyzing the reflectivity of the myocardium, has shown that the amount of fibrous tissue within the myocardium is abnormally increased in CRD patients.[59,60] It has recently been proposed that the heart study by magnetic resonance imaging and gadolinium also allows assessing the severity of myocardial fibrosis in these patients.[61] Finally, it has been published that blood levels of certain peptides derived from the type I collagen metabolism are increased in CRD patients; these peptides have been considered markers of myocardial deposition of collagen fibers.[28,59,60]

Management of hypertensive heart disease in CRD

The treatment of hypertensive heart disease in CRD patients entails two goals: the first one is to reduce high blood pressure with antihypertensive drugs having shown their capacity to repair the lesions of myocardium remodeling, to promote regression of LVH, and to preserve diastolic function; the second goal is to effectively treat the factors associated with CRD facilitating myocardium remodeling. The only three hypertensive drugs that have shown this triple capacity in clinical studies are the diuretic torasemide,[62,63] the ACEI lysinopril, [21] and the angiotensin II AT_1 receptor antagonist losartan.[22,64]

The measure aimed at correcting the biochemical and hormonal changes occurring in CRD having shown the highest efficacy from the perspective of

heart protection has been anemia correction with recombinant erythropoietin.[65] We may, however, point out that up to 10% of the patients with CRD and heart failure present erythropoietin resistance,[66] which will lead to the use of high doses with the subsequent risk for adverse events, or to use levocarnitine, which in addition improves the response to erythropoietin, may improve oxidative metabolism of fatty acids and ATP availability within the cardiomyocytes.[67] Stringent control of phosphatemia and the calcium-phosphorus product, as well as of parathormone levels, may favorably contribute to heart protection in the patient with CRD and hypertensive heart disease.[68] An increasing number of evidences suggest that the administration of vitamin D to patients with CRD and hypertensive heart disease reduces LVH and improves ventricular function through mechanisms unrelated to mineral metabolism.[69] Finally, dialysis optimization in patients on renal replacement therapy is mandatory from the perspective of heart protection, not so by increasing the clearance of potentially cardiotoxic molecules, but by preventing expansion of the extracellular volume that may unfavorably impact on a remodeled and dysfunctional myocardium through increased blood pressure.[70]

From a future perspective, we may highlight the cardio-protective pharmacological potential of urotensin II, a cyclic peptide produced in different organs, including the heart. Recent data indicate that CRD patients presenting high levels of urotensin II have less ventricular hypertrophy and dysfunction,[71] and lower risk for cardiovascular events[72] than patients with normal levels but similar prevalence of traditional risk factors. It has experimentally been shown that urotensin II decreases cardiomyocytes growth and promotes diastolic ventricular filling.[73] It would be thus interesting to study whether the use of urotensin II receptor antagonists, already available for pharmacological use,[74] is effective in the prevention and management of hypertensive heart disease in CRD.

CONCLUSIONS

Hypertensive heart disease is a common complication in hypertensive patients with poor prognosis. The lesional substrate, myocardium remodeling, is the determinant factor of the complications present in the patients with this heart disease, particularly diastolic dysfunction that progresses to diastolic heart failure. Given that CRD promotes myocardium remodeling from early stages, hypertensive patients with CRD are more prone to this heart disease and its complications. From that, we may infer that the nephrologist has to be sensible and prepared to diagnose and properly manage it, which implies the collaboration with the cardiologist to improve the health care of CRD patients, which has to definitively be institutionalized.[75] This collaboration has to extent to investigate the mechanism underlying hypertensive heart disease in CRD in order to develop more specific therapies to minimize its consequences and, in this way, improving the cardiovascular prognosis in renal patients.

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