Cardiorenal syndrome: Clinical and echocardiographic aspects

Síndrome cardiorrenal: aspectos clínicos y ecocardiográficos

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Abstract

Cardiorenal syndrome (CRS) is a disorder in which the heart and kidneys are involved, interacting, and producing a dysfunction between them in an acute or chronic way. There are different clinical phenotypes well identified as "heart and kidney disorders in which acute or chronic dysfunction in one organ induce acute or chronic dysfunction in the other." The high incidence of cardiovascular morbimortality in patients with chronic terminal kidney disease (CKD), especially heart failure (HF), initially causes a myocardial lesion that leads to ventricular remodeling, which induces the activation of compensatory mechanisms, among which the kidney is a fundamental part since it regulates the hydroelectrolytic homeostasis and thus the circulating volume, being this in the dialytic stage more evident. The functional and anatomical changes at cardiovascular level that occurs in these patients are very prevalent and include hemodynamic interactions of the heart and kidneys in HF and the impact of atherosclerotic disease in both organ systems. We also describe diagnostic and therapeutic strategies applicable to CRS, which determine the importance of echocardiography as a useful diagnostic model. Finally, we analyze the possibilities of treatment and remission of cardiac functional alterations with renal transplantation in patients with T-CKD.

Key words: Cardiorenal syndrome. Kidney transplant. Echocardiographic aspects. Systolic function. Diastolic function. Left ventricular hypertrophy.

Resumen

El síndrome cardiorrenal (SCR) es un trastorno en el que intervienen el corazón y los riñones, interactuando y produciendo una disfunción entre ellos en forma aguda o crónica. Existen diferentes fenotipos clínicos bien identificados como «desórdenes del corazón y riñón en los que la disfunción aguda o crónica en un órgano induce la disfunción aguda o crónica del otro». La alta incidencia de morbilidad cardiovascular presente en los pacientes con enfermedad renal crónica terminal (ERCT), en especial la insuficiencia cardíaca (IC), origina inicialmente una lesión miocárdica que conlleva remodelamiento ventricular, lo cual induce a la activación de mecanismos compensadores, entre los cuales el riñón es pieza fundamental, ya que regula la homeostasis hidroelectrolítica y así el volumen circulante, siendo esto en la etapa dialítica más evidente. Los cambios funcionales y anatómicos cardiovasculares que se producen en estos pacientes son muy prevalentes e incluyen las

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interacciones hemodinámicas del corazón y los riñones en la insuficiencia cardíaca, y el impacto de la enfermedad aterosclerótica en ambos sistemas de órganos. También describimos estrategias diagnósticas y terapéuticas aplicables al síndrome cardiorrenal, que determinan la importancia de la ecocardiografía como modelo de diagnóstico útil. Finalmente, se analizan las posibilidades de tratamiento y la remisión de las alteraciones funcionales cardíacas con el trasplante renal en los pacientes con ERCT.

Palabras clave: Síndrome cardiorrenal. Trasplante renal. Aspectos ecocardiográficos. Función sistólica. Función diastólica. Hipertrofia ventricular izquierda.

Introduction

Throughout its evolution, heart disease is a common complication of advanced or end-stage renal disease (ESRD), especially when it interacts with heart failure (HF), and it is the leading cause of death in patients on renal replacement therapy¹. Alterations in cardiac morphology and function are rather common in individuals with chronic kidney failure, mainly in those who are on dialysis^{2,3}. There is enough evidence that demonstrates left ventricular hypertrophy (LVH) regression and improved ventricular function after successful kidney transplant (KT), which constitutes the best therapeutic alternative for ESRD treatment, since it significantly improves life quality and expectancy of the kidney disease patient in comparison with replacement therapy⁴. Echocardiographic evaluation is an essential tool in the assessment, diagnosis, and prognosis of patients with chronic kidney failure, since it is a non-invasive study that is used to evaluate the heart structure and function⁵.

Cardiorenal syndrome (CRS)

CRS is characterized by a high degree of interactions between the heart and the kidneys^{6,7}. It is a state of advanced deregulation between heart and kidneys⁸, which entails compromise of both systemic organs⁹ due to an acute or chronic dysfunction of one of the organs that induce dysfunction of the other¹⁰, whereby physiological functions in the heart-kidney relationship will be altered, where either of both organs will use a compensation mechanism that will have an important impact on the other organ¹¹.

The definition of this syndrome has three particular characteristics that make us understand it:

- Equal relevance between both organs, since often it is unclear where the damage started
- Dysfunction can be acute or chronic, functional. or structural
- CRS has a bidirectional interaction¹².

These characteristics lead to a vicious cycle that translates into decompensation of the entire circulatory system¹³. There is close communication between the heart and the kidneys through several pathways that include renal perfusion pressure, cardiac filling pressure, and neurohormonal activity, particularly of the sympathetic nervous system, the renin-angiotensin-aldosterone system, and natriuretic peptides¹⁴.

Based on this concept, chronic kidney disease (CKD) produces heart structural and functional changes such as left ventricular (LV) dilatation, LV systolic and diastolic dysfunction, and LVH, with the latter being the most commonly observed change in patients with CKD¹⁵. LVH is the result of multiple factors: high blood pressure, volume overload, chronic uremic environment, and inflammatory, metabolic, and hormonal changes.

This was grouped in five subtypes according to disease acuteness and organs sequential involvement, as described in figure 1⁷⁻¹⁶. The goals of this CRS consensual definition were to facilitate a reliable characterization of cardiorenal deregulation clinical presentation for diagnostic and therapeutic purposes, and to rationalize epidemiological studies inclusion criteria, to identify treatment target populations, and to develop new diagnostic tools for diagnosis and management of CRS¹⁶.

Cardiovascular events in CKD

The main cardiovascular events account for almost 50% of the causes of death in patients with CKD. Cardiovascular mortality is estimated to be twice as high in subjects with Stage 3 CKD (estimated glomerular filtration rate [eGFR] between 30 and 60 mL/min) and 3 times higher at Stage 4 (eGFR between 15 and 30 mL/min), in comparison with the population with normal kidney function. However, patients at any stage from 1 to 4 have a lower degree of cardiovascular compromise in comparison with patients on dialysis. Stage 5 patients who are not on renal replacement therapy showed a similar mortality rate to those on dialysis¹⁷.

Figure 1. CRS classification (adapted from Pereira-Rodríguez et al., 2017⁷ and Rangaswami et al., 2019¹⁶). CRS: cardiorenal syndrome; ARF: acute renal failure; CKD: chronic kidney disease; LVH: left ventricular hypertrophy.

The prevalence of LVH is estimated to range between 16% and 31% in individuals with eGFR > 30 mL/min; it increases to 60-75% before starting renal replacement therapy, and it rises to 90% after dialysis is started¹⁸. The prevalence of LV systolic dysfunction varies between 15% in patients who start hemodialysis treatment and 18% for those who are on regular dialysis treatment, and it can reach 28% in those evaluated for transplantation¹⁹. Figure 2 shows the relationship between HF and chronic kidney failure.

Uremic cardiomyopathy

The myocardial remodeling that occurs in chronic kidney patients' cardiovascular disease, also called uremic cardiomyopathy, is predominantly secondary to volume and pressure overload (Fig. 3). There is big difference between general population survival and survival of patients with ESRD, due to accumulation of cardiac and vascular pathology. In Foley's epidemiologic study, 5-12% of individuals of the general population had coronary heart disease and 20% had ultrasound diagnosed LVH; conversely, of the patients with ESRD who were being started on dialysis, 40% had coronary heart disease and 75%, or even more, had LVH²⁰. The fact that these figures have been obtained at the beginning of the dialysis program accounts for the

importance of what happens before the patient is able to gain access to this procedure.

Among the structural changes, predominantly concentric LVH and valve alterations such as aortic and mitral valve calcification have been observed. As for ventricular function changes, echocardiography suggests higher diastolic (50%) than systolic dysfunction (20%) in patients on dialysis²¹. Diastolic dysfunction is caused by altered ventricular relaxation and reduced distensibility secondary to myocardial interstitial fibrosis.

LVH is the myocardial abnormality that is predominantly specific of uremic heart disease³, and it is caused by LV pressure overload secondary to increased systemic arterial resistance, to blood pressure elevation and reduced distensibility of the great vessels due to aortic calcification, which it is typical in patients with CKD; all these factors result in myocardial cells thickening and LV concentric remodeling together with intracardiac renin-angiotensin system activation; this induces hyperaldosteronemia, which promotes cardiac fibrosis through signals that induce the production of profibrotic growth factors, the vicious cycle of myocardial remodeling³⁻²².

Myocardial hypertrophy induces cell apoptosis and activates metabolic pathways capable of increasing the production of extracellular matrix until fibrosis is reached. Fibrosis leads to a progressive deterioration

Figure 2. Relationship between heart failure and chronic kidney failure (*adapted from Pereira-Rodríguez et al., 2017*⁷). KF: kidney failure; HBP: high blood pressure; DM: diabetes mellitus; ESRD: end-stage renal disease; LV: left ventricle; CV: cardiovascular; AMI: acute myocardial infarction; CVA: cerebrovascular accident; CHF: chronic heart failure.

Figure 3. Effect of heart failure on kidney function.

of myocardial wall contractility, systolic and diastolic dysfunction, dilated cardiomyopathy, and congestive HF (CHF). These changes in the heart structure lead to alterations in cardiac electrophysiology and, hence, to the development of arrhythmias¹⁷.

LVH is highly predictive of cardiovascular morbidity and mortality, in addition to being quite common among patients with CKD and, in this population, being secondary to multiple factors such as high blood pressure, volume excess, a uremic environment, and different inflammatory, metabolic, and hormonal changes.

Cardiovascular compromise is present in around 80% of patients on hemodialysis¹⁶, and 75% of

patients who are started on dialysis have LVH. The present study observed that 84.7% of the patients developed severe LVH with 3 or more years of dialysis²⁰.

As for diastolic dysfunction, it is common in CKD patients as a result of LVH and cardiac fibrosis. Similarly, diastolic function has also been shown to improve after transplantation^{23,24}.

Volume overload secondary to dialysis arteriovenous shunt, salt and water overload, anemia, coronary ischemic disease, hypertension, and hypoalbuminemia result in myocardial cell lengthening and LV eccentric or asymmetric remodeling or dilatation³.

KT, the therapeutic alternative

At present, available treatments for the management of ESRD include dialysis and KT. Dialysis modalities include hemodialysis and peritoneal dialysis, which, in turn, includes chronic ambulatory peritoneal dialysis and automated peritoneal dialysis. The selection of the dialysis modality will be influenced by a myriad of considerations to be taken into account, such as availability and convenience, comorbidities, socioeconomic status, patient's home situation, and the capability to tolerate volume changes²⁵.

KT is the treatment of choice for patients with ESRD, thus resulting in better quantity and quality of life, and lower cost for the health system than long-term dialysis^{26,27}. HF is an important cause of morbidity and mortality in patients with ESRD, with a reported prevalence among patients on dialysis of 12-36 times that of the general population²⁸⁻³⁰. In a historical cohort study with more than 1900 patients enrolled in the US Renal Data System (Dialysis Morbidity and Mortality Study, WAVE 2), the incidence of HF was 71/1000 person-years, and associated mortality 3 years after HF onset was 83%³¹. De Mattos et al.³² demonstrated a strong correlation between reduced ejection fraction (EF) and mortality in a population selected for KT waiting list, with each left ventricular ejection fraction 1-point increase being associated with a 2.5% decrease in risk-adjusted mortality. Several studies have shown that KT is the best treatment for patients with ESRD in terms of survival rate increase, reduced complications, and quality of life improvement.

KT should be discussed with all patients with progressive and irreversible chronic disease. Patients who are interested and who do not have contraindications should be referred to a transplantation program when eGFR is below 30 mL/min/1.73 m². Given that patients with ESRD have many comorbidities, it is important for them to be carefully evaluated to detect coexisting diseases that might put perioperative management and post-transplant survival at risk.

In a systematic review of 110 studies that included 1,961,904 patients with kidney failure, KT was associated with a lower risk of mortality and cardiovascular events, as well as to a better quality of life in comparison with chronic dialysis treatment. The results were consistent for the different dialysis modalities, for transplantation from both living and cadaveric donor, and between countries with different health-care systems³³.

In 2016, a study carried out in Korea over a 4-year period demonstrated that those patients on dialysis

who underwent KT showed a significant improvement in overall survival and cardiovascular results in comparison with those who remained on dialysis³⁴.

Even a study conducted by Santos et al. reported that patients with CKD of uncommon causes, such as hemolytic uremic syndrome or glomerulonephritis, had better 5-year survival than diabetic patients on dialysis, in addition to higher rates of transplantation than diabetic and hypertensive patients³⁵.

These results confirm that KT is the ideal treatment for chronic kidney failure and justify current attempts to increase the number of patients who benefit from KT all over the world.

Role of echocardiogram in cardiovascular assessment

Doppler echocardiography is a non-invasive, inexpensive, and widely available technique for evaluating cardiac structure and function by bringing together several ultrasound techniques in a single examination, although it is prone to interobserver variability³⁶.

Cardiovascular disease is a broad and heterogeneous entity, with LVH being common in KT candidates, along with LV systolic and diastolic dysfunction, heart valve diseases, and coronary artery disease. Transthoracic echocardiography is usually sufficient to detect significant LVH and LV enlargement, ventricular function, abnormalities in other cardiac chambers, valve abnormalities including mitral and aortic stenosis, and pulmonary hypertension. It is important to remember that echocardiography should be performed only after having reached dry weight and without clinical evidence of CHF.

The presence of pulmonary hypertension is associated with adverse post-transplant outcomes with regard to both graft function and patient survival. The finding of pulmonary hypertension by echocardiography may, in turn, lead to further investigations such as sleep studies and right heart catheterization.

In the case of screening for coronary artery disease in chronic kidney patients with a history of hypertension or diabetes, detecting decreased flow of the coronary sinus by echocardiography at rest has high sensitivity and specificity in the diagnosis of ischemic heart disease³⁷.

Kidney transplantation and cardiac remodeling

KT has undergone great advances in recent years and has become the treatment of choice for patients

Figure 4. Summary of the main renal and cardiovascular adverse events as a novel clinical endpoint in cardiorenal trials (reprinted with permission from Ronco et al., 2017³⁹. Copyright © 2017, S. Karger AG, Basel).

with ESRD, significantly improving life quality and expectancy of these patients, in comparison with permanent renal replacement therapy³⁸.

With KT, an adequate GFR is achieved, which corrects blood volume and reduces uremic toxins. Successful KT has been shown to be associated with significant improvements in LV mass index, ventricular function, and valve regurgitation after KT.

This both structural and functional reverse remodeling of the heart plays a critical role in cardiovascular mortality. Thus, 10% decrease in the left ventricular mass translates into 28% reduction in the risk of cardiovascular mortality¹⁷.

In a study carried out in 767 patients who underwent a transthoracic echocardiogram before transplantation, at 1 week, at 1 year, and 5 years later, LVH (defined as a mass index > 115 g/m² for men and 95 g/m² for women) was shown to occur in 71% of patients with CKD before transplantation. The prevalence of LVH decreases from 71% to 66% at 1 year and to 57% at 5 years of transplantation²⁸. In addition, the ventricular mass index decrease was shown to be 9.2 g/m² at 1 year and 19.1 g/m² at 5 years post-transplantation.

We consider supporting the need for a dedicated interdisciplinary cardiorenal team to spearhead early identification of patients with decompensated CRS and jointly manage appropriate clinical interventions at inpatient and outpatient settings³⁹.

We trust in an educational proposal to understand CRS, where cardiologists, when facing major cardiovascular events such as HF, myocardial infarction, or cerebrovascular accident, take care of kidney integrity and function; and, on the other hand, where nephrologists

have a perception and understanding of acute renal failure and ESRD as multipliers of cardiovascular risk. We need a new generation of cardiorenal physicians with a cutting-edge approach to the detection, diagnosis, prognosis, and management of CRS (Fig. 4)³⁹.

Conclusions

CRS is characterized by a high degree of interactions between the heart and kidneys. This close relationship occurs through atherosclerotic and hemodynamic factors, uremia, anemia, protein imbalance, and genetic factors. Its diagnosis is based both on laboratory data and diagnostic imaging methods such as echocardiography.

There is a critical need for guidelines and better clinical practice models from the leading cardiology and nephrology professional societies, specifically oriented to cardiorenal medicine outcomes and to the funding of research in both specialties to focus on the needs of future therapies.

KT would be a valid therapeutic alternative to reduce the elevated rates of cardiovascular morbidity and mortality in this population.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

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