

Cardiovascular Disease in Patients with Chronic Renal Failure: The Cardio-Renal Axis

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ABSTRACT

Chronic renal disease has been associated with an increase in cardiovascular morbidity and mortality. It is currently a very frequent disorder in which calcium and phosphate metabolism and myocardial hypertrophy play an outstanding role, and it constitutes an independent risk factor for cardiovascular disease. Previous clinical studies have demonstrated the consequences of the alteration in renal function on the increase of cardiovascular risk. Patients with moderate to severe renal chronic disease have an exponential increase in cardiovascular mortality, even before developing renal failure. The present study summarizes the information of basic research on the cardio-renal axis, and establishes the need of animal models to study the factors interrelated with this axis.

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Key words >

Chronic Renal Failure - Cardiovascular Diseases - Chronic Renal Failure

BACKGROUND

The interaction between heart and kidney is well-known: congestive heart failure may be associated with acute pre-renal or parenchymal renal failure, depending on the time course of development of the disease. In addition, in the seventies Linder et al. reported the association between hemodialysis and accelerated atherosclerosis. (1) Nevertheless, the relationship between renal dysfunction and cardiovascular risk has never been so evident as it is nowadays, becoming one of the greatest issues in health care. (2-4) In 1998, a group of experts of the National Kidney Foundation reported a 10 to 30-fold increase in mortality rates in patients under hemodialysis compared to general population. (5) For this reason the group of experts recommended that patients with chronic renal disease (CRD) should be considered at high risk for cardiovascular disease (CVD). (5) Sarnak et al. have informed that CVD is not only associated with CRD but also patients with this condition are more likely to die of a concomitant CVD than for their initial renal disease. (6) Relative risk is several hundreds of times greater compared with mortality in young patients in the general population and with patients of the same age in a hemodialysis program. (7) Sarnak describes that the increase in the detection of RCD and CVD constitutes an epidemic. (6) According to McClellan, life expectancy has increased in developed countries as a consequence of overcom-

ing several stages since the 19th century life. Firstly, population nutrition improved, followed by control of infections with antibiotic therapies; finally, we are now in the third stage where chronic diseases are the main causes of morbidity and mortality. (5, 8)

CARDIOVASCULAR RISK AND CHRONIC RENAL DISEASE

The importance of the new definition of CRD (3, 9, 10) is related with its early diagnosis associated with the risk of CVD; thus, different scientific societies have incorporated renal disturbances in the analysis of cardiovascular risk. In this way, the American Heart Association (AHA) adds CRD to the list of risk factors for the development of CVD. Several studies have demonstrated an increase in the prevalence of ischemic heart disease, left ventricular hypertrophy and congestive heart failure in patients with CRD compared to the general population. (9-11) In order to explain the difference between the *expected* mortality and the *observed* mortality in patients with CRD (one of the highest indexes of mortality in modern Medicine), the vascular risk factors in these patients have been classified in two groups: traditional and non-traditional risk factors.

Traditional risk factors include advanced age, male sex, hypertension, high levels of LDL cholesterol, low levels of HDL cholesterol, diabetes, smoking habits, sedentary lifestyles, menopause, left ventricular hypertrophy and a family history of CVD. *Non-tradi-*

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tional risk factors comprise microalbuminuria, high levels of homocysteine in blood, anemia, calcium and phosphorus metabolism disorders, changes PTH blood levels, treatment with vitamin D analogues, extracellular fluid volume overload, electrolytic imbalance, oxidative stress, inflammation, malnutrition, thrombogenic factors, and finally, nitric oxide/endothelin imbalance. (8, 12-16) Each day new factors appear which are potentially related to CVD in general and to CRD in particular. (15) In a longitudinal follow-up, Keith et al. studied 27,998 patients with a glomerular filtration rate lower than 90 ml/min/1.73 m² in two determinations and found a strong association between CRD and hypertension, coronary artery disease and congestive heart failure. (15) The results published by Kundhal et al. were similar. (17) Nevertheless, in the multivariate analysis, when adjusting for hypertension or diabetes, the risk of RCD *per se* decreased; however, CRD remained as an independent risk factor for mortality. (15, 17)

CALCIUM AND PHOSPHORUS METABOLISM AND CARDIOVASCULAR RISK

Block et al. studied 40,538 patients on hemodialysis and they assessed the mortality rate for CRD and its relationship with mineral disturbance (hyperphosphatemia, hypercalcemia and secondary hyperparathyroidism). Multivariate analysis for relative risk and proportional regression analysis were performed for serum phosphorus, serum calcium, calcium x phosphorus product and serum intact parathyroid hormone levels (PTH). The authors reported that serum levels of phosphorus greater than 5.0 mg/dl and PTH levels greater than 600 pg/ml were significantly associated with increased mortality for CRD and high incidence of fractures. (14) Later, other retrospective studies informed that a high calcium x phosphorus product and low levels of serum calcium - other bone metabolism parameters - should also be considered. (14, 18) This association might be related to an increase in vascular calcification in these patients, (12, 13) due to passive or active mechanisms involved in the transformation of smooth muscle cells in osteoblast-like cells. (13) The relative risk related to disorders in the calcium-phosphorus metabolism reported by the aforementioned study by Block et al., (14) was even greater than the presence of anemia or underdialysis.

LEFT VENTRICULAR HYPERTROPHY AND CYTOKINES

Vascular disease and left ventricular hypertrophy (LVH) are the most prevalent clinical presentations in patients with CRD. This review refers to the LVH considering the triggers responsible for hypertrophy of the myocyte. Studies based in molecular biology demonstrated that myocyte hypertrophy and collagen concentration are triggered by different signals, which Tarone classifies in two categories: (19)

- a) *Mechanical signals*: volume or overload pressure.
- b) *Neurohumoral signals*: angiotensin II (Ang II), transforming growth factor b (TGF- β), insulin-like growth factor (IGF), endothelin 1 (ET 1), cytokines and leukemia inhibitor factor (LIF), parathyroid hormone (PTH), and parathyroid hormone-related peptide (PTHrp), among others. (19)

Among the different types of signaling, the renin-angiotensin-aldosterone system (RAAS) plays a fundamental role in the development of myocyte hypertrophy and interstitial fibrosis by stimulating the angiotensin II type 1 receptor. (20)

Recently, Ardura et al. have published their preliminary experiences analyzing the *in vitro* interaction of similar stimuli - PTHrp, epithelial growth factor (EGF), vascular endothelial growth factor (VEGF) - in the epithelial-mesenchymal transition that takes place during the processes of renal fibrogenesis, in which VEGF is a potential mediator. (21) PTHrp might be involved in the mechanisms related with TGF- β overexpression induced by the increase of the levels of glucose in renal podocytes. (22) PTHrp may stimulate TGF- β , p27 and type IV collagen in these cells; thus, the authors suggest that it may promote glomerulosclerosis. (22) This team work also described the interaction between PTHrp with several proinflammatory pathways in kidney cells and, consequently, it may be one of the mechanisms responsible for the inflammation seen in renal damage. (23) In this way, PTHrp interrelates with other factors for the development of renal fibrogenesis, such as angiotensin II and endothelin 1 which, in turn, are related with myocyte hypertrophy. The result of the interaction of these factors on the myocyte leads to left ventricular hypertrophy and, subsequently, to an increase in the risk of CVD. (24, 25)

EXPERIMENTAL MODELS

It is evident that we need an experimental model in animals in order to study the cardio-renal axis and to develop and evaluate therapeutic tools. Few experimental models have been published: three have analyzed the cardio-renal axis in experimental animals not subjected to genetic manipulation and two performed in knockout animals. Dikow et al. ligated a coronary artery for 60 min, followed by reperfusion for 90 min in subtotally nephrectomized rats. They concluded that animals with mild impaired renal function had a reduced ischemia tolerance that was independent of hypertension, sympathetic activity or salt retention. (26) In another study (27) unilateral nephrectomy was performed in rats, followed after 1 week by a myocardial infarction (MI) achieved with permanent ligation of the coronary artery. The animals were divided into two groups, according to the degree of compromise of the left ventricle: one with a mild MI (<20%) and one with a moderate MI (>20%).

Animals with MI greater than the 40% of the left ventricle were not analyzed. Mild proteinuria up to 55.5 mg/d was observed in the first group, whereas proteinuria rose significantly higher to 124.5 mg/d in the second group, making evident the progression of renal damage as a consequence of the induction of myocardial infarction. Left ventricular pressure was correlated with proteinuria; the authors concluded that finding the underlying physiopathological mechanisms involved in cardio-renal interaction might enable improved protection for both kidneys and heart. (27) Finally, the same research team used the experimental model of unilateral nephrectomized rats followed after 1 week by ligation of the coronary artery as described previously. A week after the MI, nephrectomized rats developed proteinuria between 20 to 507 mg/d and the mean systolic pressure was 131 ± 7 mm Hg. Endothelial function - assessed as endothelium-dependant relaxing effect of acetylcholine in vessels previously stimulated with phenylephrine - predicted the severity of renal damage induced by myocardial infarction. The authors concluded that this model might be useful to develop and analyze renoprotective therapies. (28) To conclude with the review of these models, there are two models described in transgenic animals: the apolipoprotein E (APOE -/-) knockout mouse, a model documenting accelerated atherogenesis in uremia, (29) and an animal model of chronic kidney disease and metabolic syndrome that used LDLR-/- mice fed high-fat/cholesterol diets. (30) These animals presented hyperphosphatemia and vascular calcification; animals with chronic kidney disease had a poor prognosis, but those treated with bone morphogenetic protein-7 (BMP-7) had better outcomes. (30) Thus, these models of knockout mice are especially useful to study CVD associated with CRD.

During a stay at the Fundació Puigvert we have designed a simple animal model to assess the physiopathological events related with the cardio-renal interaction. This model is summarized in Figure 1: the rat is subjected to a 5/6 nephrectomy and the coronary artery is ligated to produce a myocardial infarction.

To conclude, it is evident that the relationship between the heart and the kidneys is a subject of increasing interest, as the kidneys and the heart are vascular organs which are also related with the endothelium. Epidemiological studies show that these interrelations are still closer. The development of experimental models for the assessment of the physiopathological mechanisms involved in the effects of the RCD on the heart or, on the contrary, in the effects of MI on renal function is a real necessity.

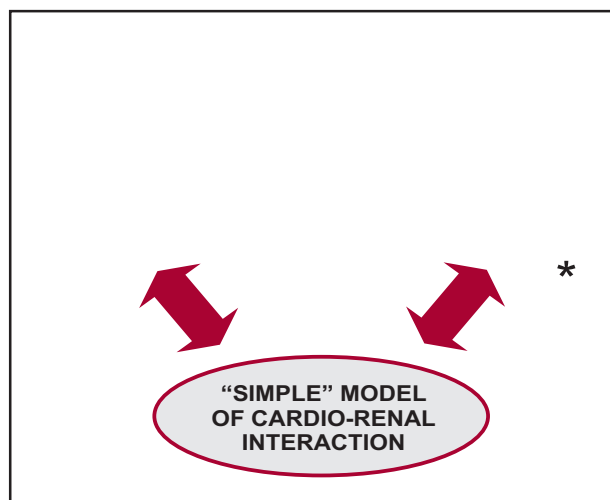


Fig. 1. Simple model of cardio-renal interaction. Surgical induction of renal failure produced by ligation of branches of the renal artery + contralateral nephrectomy + surgical induction of myocardial infarction.

RESUMEN

La enfermedad renal crónica se ha relacionado con un incremento de la morbimortalidad cardiovascular. Es una patología muy frecuente en la actualidad y constituye un factor de riesgo cardiovascular independiente, en el que el metabolismo del calcio-fósforo y la hipertrofia miocárdica tienen un papel relevante. La consecuencia de la alteración de la función renal sobre el incremento del riesgo cardiovascular se ha demostrado en estudios clínicos previos. Los pacientes con enfermedad renal crónica moderada a grave tienen un incremento exponencial de la mortalidad por enfermedad cardiovascular, incluso mucho antes de desarrollar la falla renal. En el presente trabajo se resume la información experimental básica sobre el tema del eje cardiorrenal y se plantea la necesidad de contar con modelos en animales para el estudio de los factores interrelacionados en este eje.

Palabras clave > Falla renal crónica - Enfermedades cardiovasculares
- Insuficiencia renal crónica

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