

The Kidney in Heart Transplantation, Tale of a Journey

El riñón en el trasplante cardíaco, relato de una travesía

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ABSTRACT

The aim of this update is to highlight the relationship between the heart and the kidney throughout the entire journey involved in heart transplantation.

Faced with heart transplantation, the cardiovascular and renal systems behave as mates of a journey that, at times, is difficult to determine when it starts, and that forces them to overcome different obstacles, such as hemodynamic changes, neuro-humoral and inflammatory response, surgical injury, immune reaction, and drug toxicity. This relationship can be seen as an adventure that they must inevitably share.

We will try to accompany both organs in this journey, but paying special attention to the kidney, and to describe the associations and protection and damage mechanisms generated throughout its course.

In this journey we can recognize solidarity responses to maintain the balance between both systems, but in this attempt to protect, collateral injury occurs.

Key words: Heart transplant - Heart-kidney crosstalk - Acute kidney injury - Cardiorenal syndrome - Inflammation

RESUMEN

La intención de esta actualización es destacar la relación que se establece entre el corazón y el riñón lo largo de toda la travesía que implica un trasplante cardíaco.

Frente al mismo, el sistema cardiovascular y el renal se comportan como compañeros de un viaje que, a veces, es difícil determinar cuándo comienza, y que los obliga a superar diferentes obstáculos, como los cambios hemodinámicos, la respuesta neurohumoral e inflamatoria, la injuria quirúrgica, la reacción inmunológica y la toxicidad medicamentosa. Esta relación puede verse como una aventura que indefectiblemente deben compartir.

En este viaje trataremos de acompañar a ambos órganos, pero fijando la atención especialmente en el riñón, y describir las conexiones, mecanismos de protección y de perjuicio que se generan a lo largo del recorrido.

En la travesía podemos reconocer respuestas solidarias, para sostener el equilibrio entre ambos sistemas, pero en ese intento de protección se producen daños colaterales.

Palabras clave: Trasplante cardíaco - Conexión cardio-renal - Insuficiencia renal aguda - Síndrome cardio-renal - Inflamación

INTRODUCTION

When speaking of heart transplantation (HTX) the focus of attention is placed on the transplanted organ, and the importance of the kidney in patient management and its acute and long-term evolution is perhaps disregarded.

The aim of this update is to highlight the relationship between both organs throughout the entire journey involved in HTX.

Faced with HTX, the cardiovascular and renal systems behave as mates of a journey that, at times, is difficult to determine when it starts, and that forces them to overcome different obstacles, such as hemo-

dynamic changes, neuro-humoral and inflammatory response, surgical injury, immune reaction, and drug toxicity. This relationship can be seen as an adventure that they must inevitably share.

We will try to accompany both organs in this journey, but paying special attention to the kidney, and to describe the associations, and protection and damage mechanisms generated throughout its course.

Briefly, we can define three stages:

Stage 1. It refers to the pre-surgical period and the impact of heart failure (HF) on renal function, with the adjustment mechanisms adopted by both organs to preserve the hemodynamic and internal environment balance.

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Stage 2. It corresponds to the immediate postoperative period, and involves the hemodynamic and inflammatory changes accompanying surgical injury.

Stage 3. It is associated with the long-term postoperative period, the effect of immunosuppressive drugs and the prognostic impact of renal insufficiency (RI) on long-term survival.

The heart and the kidney have a close association, and changes in one generate a response in the other, a reaction that occurs in both senses, establishing a bi-directional relationship. The responses are sustained and amplified, developing a circuit that tends to be enhanced and sustained over time. This circuit tries to maintain cardiovascular and renal stability, preserving blood pressure and kidney perfusion, but it also has negative effects at both ends of the circuit, generating renal hypoxia, volume overload and HF. The relationship tends to homeostasis, but at the expense of collateral damage.

The association between the heart and the kidney, in addition to hemodynamic mechanisms, is established at several levels, producing neurohumoral and inflammatory responses, changes in the acid-base state and body fluids, bone metabolism disorders, anemia and nutritional abnormalities.

When speaking of the link between these two systems it is necessary to discuss the cardiorenal syndrome (CRS). This term refers to the concomitant disorders of both systems, and that the pathological condition of one system affects the other. In the 2008 Acute Dialysis Quality Initiative (ADQI) conference, five types of SCR were defined and classified: (1)

CRS type 1: Acute cardiorenal syndrome, when acute HF produces acute RI.

CRS type 2: Chronic cardiorenal syndrome, when chronic HF progressively leads to chronic RI.

CRS type 3: Acute renocardiac syndrome, when acute RI produces acute HF.

CRS type 4: Chronic renocardiac syndrome, when chronic RI leads to structural and functional heart disorders.

CRS type 5: Cardiorenal syndrome secondary to a systemic cause producing HF and RI.

This classification considers two aspects: the first is identifying the organ that fails in the first term and is held responsible for the problem, and the second is whether the dysfunction is acute or chronic.

This classification helps to interpret the clinical condition, has relevance as a first approach to the problem, but the patient cannot always be placed in one of the CRS types and neither is it easy to establish whether the condition is acute or chronic.

First stage of the journey

The first stage is dominated by advanced HF that leads to HTX. It concerns patients who have exhausted the therapeutic possibilities and, at the time of transplantation, are usually under inotropic therapy and circulatory or respiratory assistance that may worsen

hemodynamic and renal stability. When, as frequently occurs, there is concomitant RI, they become CRS type 1 or type 2, according to the time of HF evolution, in which neurohumoral and inflammatory responses are developed.

Hemodynamic and neurohumoral response

In normal conditions the kidneys receive 20-25% of cardiac output (CO). In advanced HF, CO is generally reduced and if there were no adaptation mechanism, renal blood flow and glomerular filtration rate would fall. Renal perfusion pressure (RPP) depends on the pressure gradient established between mean arterial pressure (MAP) and central venous pressure (CVP) [$RPP = MAP - CVP$]. Cardiac output depends on preload, afterload, contractility and heart rate.

In advanced HF, reduced CO or an insufficient CO to fill the vascular bed causes decreased RPP, leading to the development of compensatory mechanisms to avoid this unwanted effect. Reduced CO and renal flow stimulate carotid sinus, aortic arch and juxtaglomerular apparatus receptors, which through neurohumoral pathways activate the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), increasing non-osmotic vasopressin secretion. This leads to water and sodium retention, and by renal afferent arteriole vasoconstriction decreases renal perfusion and its excretory function. Angiotensin II, through a non-osmolar mechanism, stimulates antidiuretic hormone secretion and enhances the neurohumoral response. By binding to its receptors it activates reactive oxygen species that can produce hypertension, arrhythmias and cell death. (2)

Despite the drop of renal blood flow, glomerular filtration can be maintained for a time, but if neurohumoral overstimulation continues, arteriolar vasoconstriction and renal hypoperfusion lead to hypoxia and structural kidney injury. (3)

As previously mentioned, the second component of RPP is CVP. Left heart failure, by definition with elevated pulmonary capillary pressure, can generate pulmonary arterial hypertension and right ventricular failure and increased CVP, thus reducing the (MAP-CVP) gradient, essential to maintain adequate renal perfusion.

Renal congestion, in addition to decreasing renal blood flow, produces intravascular fluid leak towards the extravascular space reducing the effective CO and producing RAAS stimulation, leading to hydrosaline retention. Briefly, the already present neurohumoral stimulation is enhanced and preserved. (4)

When right heart failure is more severe, renal congestion is accompanied by abdominal organ congestion, increased intraabdominal pressure and renal venous pressure, with the ensuing decrease of renal perfusion. Kidney failure secondary to advanced HF is the rule in patients facing HTX. It should be mentioned that in many cases of acute HF there is also increased CVP, and that in patients presenting CVP >24 mmHg, up to

70% develops RI during hospitalization. (5,6)

Inflammatory response

In this stage of the journey, the inflammatory response accompanying HF plays an important role. Activation of the sympathetic nervous system and RAAS increases the presence of proinflammatory molecules in the heart and kidney, causing hemodynamic and structural changes in both organs. Circulating cytokines produce vasodilation, hypotension and can lead to cardiac remodeling, fibrosis and ventricular function impairment. (7,8)

Under adrenergic stimulation, activated mononuclear cells, the injured myocardium and the hypoperfused peripheral tissues are the sources of cytokine production. Bacterial translocation and endotoxin release by edema and intestinal ischemia is another postulated mechanism. Among all the proinflammatory cytokines, the most studied and associated with HF are interleukin (IL)-6, IL-1 and tumor necrosis factor α (TNF α). (9,10)

IL-1 has been isolated in the myocytes of patients with idiopathic dilated cardiomyopathy and produces depressed contractility, arrhythmia and apoptosis. IL-6 blood concentration is elevated in patients with HF and generates myocytic hypertrophy and ventricular dysfunction. (11)

The elevation of TNF α in the blood of patients with HF causes ventricular dysfunction, apoptosis and participates in the development of cardiac cachexia. (12-14)

Inflammatory activity in HF has been measured with different serum markers, such as C reactive protein (CRP), myeloperoxidase, intracellular adhesion molecules (ICAM) and lately by non-codifying ribonu-

cleic acid molecules (microRNA). (15-18)

The relationship between inflammatory markers and HF emerges mainly from observational and retrospective studies, with contradictory conclusions that hinder their transfer to clinical practice, and drugs with proven anti-inflammatory effect in HF, such as corticosteroids, statins, TNF α blockers or immunoglobulin do not show benefits in clinical endpoints. (19)

It is accepted that the inflammatory response is associated with worse prognosis, both in HF with reduced as preserved function, but causality has not been demonstrated, and probably should be interpreted as a risk marker. (20,21)

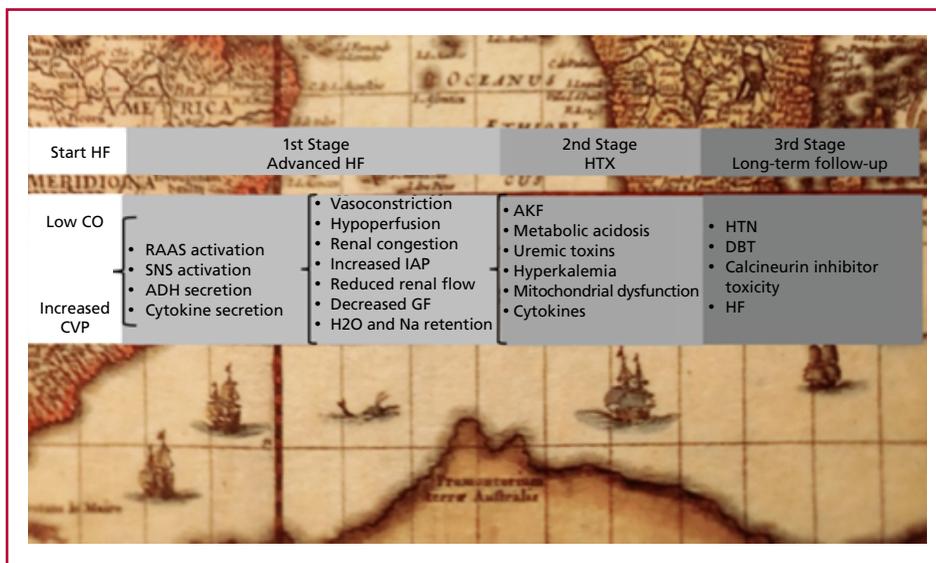
Continuing with this allegory, it can be said that the “renal ship” has concluded the first stage of this voyage, but it does not arrive unscathed: renal function in patients with advanced HF is abnormal almost without exception. Through the already explained mechanisms, the hemodynamic changes of HF, and the neurohumoral and inflammatory response, always affect renal function in a different degree. The route can be followed in the roadmap (Figure 1).

Second stage of the journey

In these circumstances the kidney must face the second stage, which is HTX and the immediate postoperative period. An unstable ship has to weather the storm that HTX means.

Acute kidney injury (AKI) is a frequent complication with up to 30% incidence after cardiac surgery with cardiopulmonary bypass (CPB), and 1% of patients may require kidney replacement therapy. It has been shown that minimal changes in postoperative creatinine levels are associated with worse survival, and HTX does not escape this rule (22-24)

Fig. 1. Roadmap of the renal journey



HF: heart failure, HXC: heart transplantation, CO: cardiac output, CVP: central venous pressure, RAAS: renin-angiotensin-aldosterone system, SNS: sympathetic nervous system, ADH: antidiuretic hormone, IAP: intra-abdominal pressure, GF: glomerular filtration, H2O: water, Na: sodium, AKI: acute kidney injury, HTN: hypertension, DBT: diabetes

In addition to patient age and diabetes, and technical aspects such as type of surgery, CPB time, and myocardial preservation, the predisposing factors to develop AKI after cardiac surgery include HF, impaired ventricular function, circulatory assistance and prior abnormal renal function which, as already mentioned, are systematically present in HTX. In addition, preoperative pulmonary hypertension has been also identified as a predisposing factor for the development of AKI. (25)

AKI in the postoperative period of cardiac surgery and HTX

The causes producing AKI in surgery with CPB can be classified as preoperative, intraoperative and immediate postoperative. Preoperative causes are due to the above mentioned hemodynamic and inflammatory effects of advanced HF and prior kidney disorder, in addition to the use of drugs that hamper renal autoregulation, as those acting on RAAS, renal vasoconstriction produced by some inotropic agents, and the nephrotoxicity of contrast solutions. (22,26)

The accepted intraoperative causes are decreased renal perfusion during CPB, absence of pulsatile flow and the hemodynamic effect of anesthetic and vasoactive drugs, together with the inflammation prompted by the surgical injury and CPB. In the immediate postoperative period, hemodynamic instability, volume depletion, nephrotoxic substances, infections and the inflammatory response are all factors that can lead to AKI. (27-29)

Acute kidney failure frequently develops in the postoperative period of HTX. In a series of 112 HTX performed by our team, classified according to KDIGO criteria, only 27% did not develop AKI, 29% presented AKI 1 (1.5 to 2-fold increase of baseline serum creatinine within 7 days), 16% AKI 2 (2 to 3-fold creatinine increase) and 26% AKI 3 (more than 3-fold creatinine increase or kidney replacement therapy). Twenty-four percent of patients required kidney replacement in the postoperative period. Presence of AKI using this classification showed a rising in-hospital and 1-year mortality gradient. (30)

Other studies agree with the elevated frequency of AKI after HTX and its immediate and long-term prognostic importance. (31,32)

Acute renal failure can produce cardiac dysfunction through several pathways. It is accepted that RAAS activation generates arteriolar vasoconstriction and hydrosaline retention that cause HF. The SNS activation, in addition to stimulating RAAS, prompts myocyte hypertrophy and apoptosis and increases myocardial oxygen consumption. (33)

Inflammatory activity also increases in AKI. Kidney injury activates renal inflammatory cells, releasing proinflammatory cytokines, such as different interleukins, interferon, TNF α and tumor necrosis factor-like weak (TWEAK), with a depressant effect on ventricular function. (34-36)

Metabolic acidosis produces myocardial depression, electrolytic abnormalities favor the emergence

of arrhythmias, and increased urea and uremic toxins cause endothelial dysfunction, vascular injury and enhanced inflammatory activity. (37)

It has been shown that in experimental AKI mitochondrial activity decreases, with lower capacity of producing high energy phosphates, which at the myocardial level reduces contractility and generates apoptosis. (38)

It is clear that AKI in the postoperative period worsens HF, and as we have seen HF causes and worsens KF. See the roadmap (Figure 1).

Third stage of the journey

After the storm of HTX and its immediate postoperative period, the kidney enters stage 3, sailing through calmer waters, though not devoid of risks. (Figure 1) We should mention the sustained effect of risk factors on the kidney, as hypertension and diabetes, that can alter its function and structure. These factors can already be present and be the cause of the heart disease leading to HTX, as in ischemic or hypertensive heart disease, or could have developed after transplantation due to the effect of medication or the HF produced by graft vascular disease or rejection.

The progress in immunosuppressive agents was essential to improve the results of HTX, but they have adverse effects. Calcineurin inhibitors, such as cyclosporine and tacrolimus can generate nephrotoxicity with characteristic anatomopathological findings. The initial mechanism is vasoconstriction of the glomerular afferent arteriole, with renal hypoxia that in early stages can be reversible and usually improves with drug reduction or discontinuation. However, it can lead to arteriopathy with PAS positive subintimal and periadventitial hyaline deposits, similar to those observed in hyaline atherosclerosis, evolving with progressive luminal occlusion, which in turn causes renal and interstitial ischemia and diffuse or band interstitial fibrosis and RI. (39,40)

Although RI can occur in the first stages of HTX, it is one of its long-term complications, generally presenting months or years after the intervention. It is a cause of death, but well below that of neoplasms and graft vascular disease.

According to the International Society for Heart and Lung Transplantation (ISHLT), its incidence has decreased over the years. In the analysis of more than 30 000 HTX, the 5-year incidence of severe RI (serum creatinine >2.5 mg/dL, dialysis or kidney transplant) in the 1994-2003 period was 25%, and in the 2004-2013 period, it decreased to 15%. The predisposing factors identified for the development of long-term RI were the need for dialysis or reoperation prior to hospital discharge, use of mechanical circulatory assistance, need for multiple inotropic drugs during hospitalization and some receptor characteristics, such as age >50 ears and baseline creatinine >1.5 mg/dL. (41)

Preservation of adequate renal function throughout this journey largely depends on adequate medical care, that the patient reaches HTX at the right mo-

ment, without excessive kidney injury, preoperative care and close follow-up monitoring.

Epilogue

Kidney behavior in HTX, both in the preoperative as postoperative stages constitutes an exceptional model that identifies the close associations between the cardiovascular and renal systems. The kidney can be seen as a traveler that must go through several difficulties to keep an adequate function and ensure a good prognosis in the transplanted patient. In this voyage there are solidary responses to maintain the balance between both systems, but in this attempt to protect, collateral damage also occurs.

It may be thought that this tale is far away from the classical form in which a scientific text is usually written. I have always believed that the scientific content must be rich and accurate, but, regarding form, I allow myself to quote and adopt the expression that says: *"I love books that speak as men more than men that speak as books"*. (42)

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

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