

# Combined Cardio-Renal Failure: a Key Factor in Heart Failure Progression and Therapy

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Cardiovascular disease is the primary cause of morbidity/mortality in the Spanish setting, justifying the extraordinary research effort being made to determine its etiopathogenesis, to predict its prognosis, and to improve treatment. In recent years there has been growing recognition of the role of kidney failure in the overall prognosis of cardiovascular disease.<sup>1</sup> Varying in severity, kidney failure very commonly accompanies heart failure, and recent work suggest it may predict the risk of death in congestive heart disease better than either the ejection fraction or the New York Heart Association (NYHA) classification.<sup>2</sup>

In this issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA, Grigorian-Shamagian et al<sup>3</sup> analyze the role of kidney failure as a predictor of heart failure mortality. Their data, although collected only in hospitalized patients, bring to light information of interest to this important topic. To begin with, this is the first Spanish study on this issue that analyzes a large number of patients (n=522). Secondly, unlike other studies in which only systolic dysfunction is taken into account, the present work examines patients with both preserved and reduced systolic function. From a clinical standpoint, the results provide useful information highlighting the importance of kidney dysfunction in the progress of heart failure.

How does kidney failure worsen the prognosis of heart failure? Among the patients examined by Grigorian-Shamagian et al, those with severe kidney failure—a problem seen among members of the subgroups with preserved and (especially) reduced systolic function—had a poorer prognosis. It should be noted that until now there have been no studies that describe possible differences in kidney function in subgroups of this type. Large scale

studies such as HOPE<sup>4</sup> and HOT<sup>5</sup> have shown that, independent of its etiology, kidney failure increases the risk of cardiovascular disease and of death from such disease. In a Spanish study involving subjects with high blood pressure who had undergone follow-up for 10 years, 14.6% suffered kidney failure (creatinine clearance [CCr] <60 mL/min).<sup>6</sup> Those who developed this problem showed a cardiovascular event rate 2.5 times higher than those with preserved kidney function. In fact, the JNC-7 identified a glomerular filtration rate (GFR) of <60 mL/min as a major risk factor for cardiovascular disease.<sup>7</sup> However, it is important to point out that the exact mechanisms behind the mutual potentiation of cardiovascular and kidney disease remain unclear. Current thinking in this area is still largely conjectural; in fact, there is no sufficiently solid experimental or clinical information that allows definitive conclusions to be drawn. It is evident, however, that a number of factors are involved in this combined failure, e.g., difficulties in the maintenance of fluid and electrolyte equilibrium, traditional and non-traditional risk factors such as hyperhomocysteinemia, an elevated Ca<sup>2+</sup>/P product, parathormone excess, anemia,<sup>8,9</sup> increased levels of circulating cytokines, and increased levels of nitric oxide synthase inhibitors such as asymmetric dimethylarginine.

As proposed by some authors, the relationship between kidney and heart failure may be bidirectional. Thus, kidney failure might accelerate heart failure, and heart failure may influence the development of kidney failure. This is in line with clinical impressions recently reported by other groups,<sup>9</sup> although systematic studies are needed to clarify the limits of this association.

In recent years, the term cardiorenal failure has been coined to refer to this joint dysfunction. This not only highlights the connection between the 2 problems but underlines the need for treatment that differs to that for heart failure or kidney failure on its own.<sup>1</sup> In patients with cardiorenal failure, heart failure and kidney failure need do not necessarily need to be symmetric either in their severity, natural history or clinical progression. This means there is a wide range of possible heart and kidney failure combinations; indeed, the types of kidney failure involved may be very different, e.g., acute and chronic kidney failure. In patients with cardiorenal failure, the

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kidney usually has organic disease (as part of a generalized cardiovascular disease) but is also functionally affected as a consequence of ventricular failure or of changes in the treatment and compartmental distribution of fluids. It is important to remember that age and renal sclerosis are not only associated with the loss of functional nephrons (up to 30% in people aged over 50 years), but also with a reduced vasodilatory response, although the capacity for vasoconstriction is maintained. Similarly, kidney dysfunction hinders the elimination of liquids in the presence of a dysfunctional heart, closing the pathogenic circle. It should be borne in mind that the recovery of myocardial function is remarkable in some patients with advanced heart disease when dialysis or ultrafiltration is provided.<sup>1</sup>

The fact that up to 56.5% of the patients in the study by Grigorian-Shamagian et al had a GFR of <60 mL/min/1.73 m<sup>2</sup> calls to attention the magnitude of this problem. This percentage is almost identical to that published in a recent study from the UK (57%).<sup>10</sup> In this context, kidney failure not only modifies the control of liquids but also the relationship of the salt/water balance with the patient's hemodynamics, as well as the therapeutic response, particularly with respect to diuretics.

In agreement with another general trend,<sup>9</sup> the study of Grigorian-Shamagian et al confirms the significant relationship between anemia, kidney function and heart failure. However, their data are cross-sectional and further studies are required to obtain information on changes over time if certain key questions are to be answered: whether stabilization of kidney dysfunction in patients with heart failure has a favorable influence on anemia, and, vice versa, whether the correction of anemia can improve the survival of patients with heart failure and reduce the kidney function deterioration rate.

Several important questions regarding anemia in CHF remain. For example, we still need to know the characteristics of anemia in functional kidney failure, to determine the variations of erythropoietin (EPO) requirements over the clinical progression of kidney failure, and to establish the behavior of endogenous EPO production and the erythroid response in individuals with severe cardiorenal failure.

It is important to point out that patients present with more subtle clinical characteristics than previously thought. Indeed, there have been series of patients in which 45% had hematocrit levels of <36% and 8% had values <30% even though their blood creatinine (Cr<sub>p</sub>) levels were <2 mg/dL.<sup>11</sup>

This highlights the importance of the method used to measure kidney dysfunction. From a strictly practical standpoint, it is clear that the GFR needs to be at least estimated and that guiding oneself by the Cr<sub>p</sub> level is insufficient; it should be remembered that the GFR has to be reduced by nearly 60% before there is any clear reflection of a problem in the Cr<sub>p</sub> levels. Grigorian-

Shamagian et al. call attention to the considerable number of patients with moderate kidney failure but with apparently normal Cr<sub>p</sub> levels—something particularly noticeable in older patients. For example, the group with a CCr of 30-60 mL/min had a Cr<sub>p</sub> of 1.4±0.3 mg/mL, a value that might easily pass unnoticed by an untrained observer. The lack of reliability of the Cr<sub>p</sub> as a true reflection of kidney function highlights the importance of being able to count on easily used methods for calculating the CCr. Currently, the use of the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD 1 and 2) formulae, are gaining ground in many cardiology units. The former tends to underestimate the GFR while the MDRD equations, although more complex and traditionally used in patients with established kidney failure, have been validated for both the healthy population and that with heart failure.<sup>12</sup> In addition, they do not require knowledge of the patient's bodyweight. However, they do tend to underestimate the GFR. In any event, given the consequences of undiagnosed kidney failure—which goes by the graphic name of *hidden kidney failure*—the key is to always determine the GFR in patients with heart failure. This latter term attempts to draw attention to patients who, because of their body weight or reduced muscular catabolism, show Cr<sub>p</sub> values in the normal range (or only slightly elevated), but who have a considerably reduced GFR.

An additional observation of interest in the work by Grigorian-Shamagian et al is that the prescription of angiotensin converting enzyme (ACE) inhibitors for patients with kidney failure attenuates the negative impact of the latter on cardiovascular prognosis. This agrees with observations made in patients with ischemic heart disease<sup>13</sup> or those with high blood pressure that develop kidney failure.<sup>6</sup> When using ACE inhibitors it is critical to determine the effective circulating volume (ECV). Although homeostatic mechanisms protect against a reduction in this volume, they do so at the cost of the kidney acquiring maximum dependence on the renin-angiotensin-aldosterone system; this organ therefore becomes more sensitive to treatment with ACE inhibitors. In addition, neurohormonal adaptation leads to overstimulation of the volume conservation mechanisms, hindering the maintenance of liquid and electrolyte balance. This implies the obligatory retention of an abnormally high proportion of the water and salt intake, making edema inevitable if not controlled. It is therefore recommendable that the starting dose of ACE inhibitors be low in patients with cardiorenal failure. Moreover, before administering ACE inhibitors it might be of interest to ensure that the depletion of the ECV is not maximal (at least in a transient fashion). This can be achieved either by reducing the administration of diuretics or allowing a brief and controlled salt intake. An additional measure that might be undertaken in patients with heart and kidney failure is to give preference to ACE inhibitors with short

half lives (e.g., captopril) or which do not require renal metabolism (e.g., furosemide). From a more general point of view, it can be said that there are two subpopulations of patients with cardiorenal failure distinguished by their response to treatment with ACE inhibitors: those that require high concentrations of angiotensin II to preserve the GFR (and which therefore tend to become worse with ACE inhibitors), and those with a deteriorated GFR due to decompensated heart failure (who improve with ACE inhibitors). Thus, although Grigorian-Shamagian et al do not provide data on the ECV of their patients prior to treatment, they do contribute interesting information to the debate on the use of ACE inhibitors, an area in which data are currently scarce.

Other treatments may need to be used more rigorously in cardiorenal failure, the most important being the use of diuretics. Two important points should be borne in mind: 1) the presence of kidney failure alongside heart failure suggests that high doses of loop-acting diuretics should be used, and that these could be advantageously administered by infusion, and 2) combinations of diuretics that act on different segments of the nephron remain the foundation of treatment. Although a CCr value of <30-40 mL/min suggests that thiazide diuretics should not be used without the support of loop-acting diuretics, it is not an express indication that either the former or distal diuretics be suspended; these could still contribute to the potentiation of the effect of furosemide or torsemide.

The presence of cardiorenal failure has redoubled interest in new therapeutic tools that offer the possibility of inducing diuretic and/or natriuretic effects without favoring prerenal failure through the depletion of the ECV, or the electrolytic problems typically associated with the use of diuretics. We are now on the eve of the generalized clinical use of arginine-vasopressin antagonists, colloquially known as "vaptans." There are currently 2 types: antagonists of V2 receptors (such as tolvaptan) which exclusively affect the elimination of water by the kidney, and those that combine antagonism against V2 and V1a receptors (such as conivaptan), which oppose the systemic vasoconstriction effect of arginine-vasopressin (potentially important in heart failure). These agents are most useful in two clinical scenarios: when patients have hyponatremia (which they can drastically improve), and when they develop resistance to loop-acting diuretics (especially in the presence of the braking phenomenon).<sup>14</sup> In general, the benefit that might be expected from this new type of drug includes increased cardiac output, a reduction in total peripheral resistance and mean blood pressure (a result of V1a antagonism), a reduction of congestion, diminished preloading, and an increased plasma sodium concentration (an effect of V2 antagonism). In a recent study,<sup>15</sup> the effects of tolvaptan (30 mg, once per day) were compared for the first time with those of furosemide (80 mg/day) in a group of patients with

mild-moderate heart failure. The results showed that, although the diuretic effect was similar, furosemide reduced kidney blood flow and tended to cause alterations in plasma sodium and potassium. No such comparative data have been published for patients with more severe heart failure.

A second group of drugs with applications in cardiorenal disease includes the recombinant human natriuretic peptides ANP (carperitide) and BNP (nesiritide). These compounds, which have been used in the treatment of decompensated heart failure, are under investigation to determine the levels of myocardial and renal protection they offer in different circumstances predisposing towards combined failure (e.g., in heart surgery).<sup>16</sup> However, doubts exist regarding the usefulness of these drugs in the presence of kidney failure, and it has even been proposed that the latter could be made worse or be induced by nesiritide. However, a recent study showed that this drug had no significant influence on renal function.<sup>17</sup>

A final group of agents to bear in mind, not just for their antianemic action but for their protective effect on kidney and heart cells, is that of the erythropoiesis stimulating agents (ESA). The recognition of the value of avoiding anemia in cardiorenal failure<sup>8,10</sup> is leading toward greater use of ESA and intravenous iron, mainly in the form of iron gluconate or saccharate. The use of ESA is in line with a new concept in the treatment of heart and kidney failure in which hemodynamic effects are associated with cell-protective and regenerative actions.

The early identification of patients with both cardiovascular disease and kidney failure is the cornerstone that allows their prognosis to be modified. The treatment of patients with cardiorenal failure requires efficient collaboration between cardiologists, nephrologists and internal medicine specialists. Understanding the best balance that can be achieved for each individual requires knowledge on homeostatic adaptation mechanisms to help treat and prevent oscillation between relatively full and empty phases of extracellular volume replenishment. These lead to cardiac decompensation and decreased renal perfusion, which in turn causes a deterioration in kidney function. Therapeutic strategies should be guided by the possibilities of obtaining realistic goals. Thus, when a patient suffers severe systolic dysfunction, the best course of action might simply be to try to prevent dyspnea at rest. A patient with tricuspid disease and anasarca might best be managed by reducing edema only to the point that it no longer interferes with normal daily life. However, the time patients need and that which doctors and hospitals have to give may not match. The time required to see any changes and to achieve equilibrium in a patient is very often incompatible with the demand for rapid discharges. A strong connection between hospitals and the primary assistance structure is therefore essential. Directly related to the work of Grigorian-Shamagian et al, it is important to point out that insufficient information is available on

combined heart and kidney failure treated by family doctors and cardiologists in the primary setting. A prospective study that would analyze this would be of great epidemiological and physiopathological interest.

The provision of relevant information to the physician who will treat patients with cardiorenal failure after their discharge—but also to patients themselves so that they can manage their own care—should be of the highest priority. It is in this area where great success may be obtained, but also where great errors could be made. During extra-hospital progress, the quality of the discharge information (so infrequently taken into account) and direct communication between the hospital and the physician treating the patient, become a valuable aid in attaining the objectives set. An explanation of why one drug or dose was chosen over another could provide useful information for patient care outside the hospital. Educating patients and their families about eliminating the use of non-steroidal anti-inflammatory drugs or what to do when faced with potentially decompensating events could also have an excellent preventive impact.

In conclusion, it is important that physicians understand that patients with combined kidney and heart failure have problems that are more than the sum of these diseases alone. The management of these patients cannot, therefore, be based on treating both diseases as separate entities. Many factors have to be taken into account and a balance sought between renal and hemodynamic factors for each individual. As recent evidence shows,<sup>3,6,7,13</sup> getting this balance right could favorably modify a patient's prognosis.

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