Cardiorenal syndrome, a pathophysiologic state in which primary dysfunction of one organ induces or exacerbates dysfunction of the other, occurs through multiple mechanisms that demonstrate the complex interaction between the two organs. The syndrome is receiving increasing attention owing to the multitude of epidemiological observational studies that correlate cardiovascular morbidity and mortality with reduced kidney function in congestive heart failure (CHF) and coronary artery disease patients. In addition, patients with chronic kidney disease (CKD) are known to have a significant increase in cardiovascular morbidity and mortality. Most of them die of such causes before reaching end stage kidney failure.

The underlying pathophysiological mechanisms have not been fully elucidated yet. Nevertheless, several potential sequences of events may arise following dysfunction of the heart or the kidney as the original insult. Recently, Ronco et al. proposed a classification of cardiorenal syndrome into five subtypes that take into account the timeframe, pathophysiology, and nature of concomitant cardiac and renal dysfunction (Ronco C, et al. *Am Coll Cardiol* 2008; 52:1527–39). It has also been suggested that the term “renocardiac” syndrome be used when the enhancement of cardiovascular death is initiated by kidney disease in contrast to cardiorenal syndrome, when the initiating event is heart disease (Schrier RW. *Nat Clin Pract Nephrol* 2007; 3:637).

The Kidney Cardiac Link

**The Cardiorenal Syndrome: Which Came First—the Chicken or the Egg?**

By Elwaleed Elhassan, MD, and Robert Schrier, MD

Cardiorenal syndrome can be defined as a pathophysiologic state in which primary dysfunction of one organ (the heart or the kidney) induces or exacerbates dysfunction of the other. Cardiorenal syndrome occurs through multiple mechanisms that demonstrate the complex interaction between the two organs.

The syndrome is receiving increasing attention owing to the multitude of epidemiological observational studies that correlate cardiovascular morbidity and mortality with reduced kidney function in congestive heart failure (CHF) and coronary artery disease patients. In addition, patients with chronic kidney disease (CKD) are known to have a significant increase in cardiovascular morbidity and mortality. Most of them die of such causes before reaching end stage kidney failure.

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The kidney in cardiac dysfunction

Deterioration of kidney function in the setting of heart failure is common and is associated with adverse outcomes and prolonged hospitalizations. The inciting mechanisms are not fully recognized but may be related to hemodynamic disturbances secondary to pump failure whereby reduced renal perfusion disrupts the filtration pressure and reduces the glomerular filtration rate (GFR). Furthermore, increased cardiac preload causes renal congestion with elevated interstitial and venous pressure of the kidney, possibly in part because of the rigid renal capsule (Schrier RW. *J Am Coll Cardiol* 2006; 47:1–8). This may further jeopardize the GFR and stimulate the renin-angiotensin-aldosterone system (RAAS) (Figures 1 and 2). Even slight decreases in estimated GFR were found to significantly increase mortality risk. So renal dysfunction is considered not only a marker of severity of cardiac failure but also a pathogenetic factor in causing progression of functional cardiac deterioration.

The primary function of the kidney is to regulate extracellular fluid volume (ECF) homeostasis. Slight deterioration of kidney function impairs the ability to maintain ECF volume and results in salt and water retention that subsequently leads to ECF volume expansion. ECF volume expansion can increase cardiac preload and lead to cardiac dilatation, which can have critical effects on heart function. Cardiac dilatation causes myriad consequences. Myocardial remodeling creates a degree of relative ischemia as well as functional mitral valve insufficiency that may contribute to pulmonary hypertension and impair left and right ventricular function.

In normal individuals, cardiac dilatation is associated with an increase in cardionic natriuretic peptides that serve to facilitate sodium balance by augmenting natriuresis. In addition, an increase in left atrial pressure decreases renal sympathetic tone and suppresses the release of the antidiuretic hormone arginine vasopressin leading to a water diuresis. These atrial-renal reflexes, which normally enhance renal sodium and water excretion, are impaired during CHF. This blunting is more established in advanced CHF as a result of decreased renal perfusion pressure and diminished sodium delivery to the distal nephron site of natriuretic hormone action. Moreover, volume overload can increase transmural myocardial pressure and increase left ventricular mass index. Left ventricular hypertrophy (LVH) is a major cardiovascular risk factor with increased mortality relating to systolic and/or diastolic dysfunction, arrhythmias, ischemic events, and sudden death.

The RAAS is known to be activated in patients with CHF. The major drive for RAAS activation is believed to be stimulation of the juxtaglomerular apparatus via decreased baroreceptor sensitivity in patients with chronic heart failure can worsen cardiac function by increasing renin-angiotensin-aldosterone system (RAAS) and sympathetic activity, enhancing proximal fluid reabsorption, impairing aldosterone escape, and blunting the response to natriuretic peptides. Na = sodium. (From reference 3).

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**Figure 1**

- **Increased Cardiac Filling Pressure**
- **Sodium or Water Retention**
- **Resistance to Natriuretic Peptides**
- **Failure to Escape from Aldosterone**
- **Decreased Distal Na and Water Delivery**
- **Decreased Baroreceptor Sensitivity**
- **Sympathetic and RAAS Activity**
- **Proximal Tubule Sodium and Water Reabsorption**

**Figure 2**

- **Increased Cardiovacular Morbidity and Mortality**
- **Vascular and Myocardial Calcification**
- **Phosphate Retention**
- **Increased Parathyroid Hormone**
- **Left Ventricular Hypertrophy**
- **Renal Insufficiency**
- **GFR < 60 mL/min/1.73 m^2**
- **Sodium Retention**
- **Inflammation**
- **Oxidative Stress**
- **Atherosclerosis**

Multiple pathways whereby chronic renal parenchymal disease may increase cardiovascular morbidity and mortality by causing hypertension, atherosclerosis, and/or myocardial dysfunction. GFR = glomerular filtration rate. (From reference 3).
The Chicken or the Egg
Continued from page 9

Increased angiotensin and decreased natriuretic oxide in the brain have been implicated as mediators of the blunting of baroreceptor sensitivity in experimental CHF. The increase in renal sympathetic tone can cause sodium retention by several mechanisms (Figure 1). Angiotensin and renal sympathetic nerve stimulation both activate receptors on the proximal tubule epithelium, which enhances sodium reabsorption. The resulting decreased sodium delivery to the distal nephron impairs the normal escape mechanism from the sodium-retaining effect of aldosterone.

The renal vasconstriction of the glomerular efferent arteriole by angiotensin II in CHF also alters net Starling forces in glomerular efferent arteriole by angiotensin mechanism from the sodium-retaining effectors on the proximal tubule epithelium, neurogenic and renal sympathetic nerve stimulation both activate re-
ceptors on the proximal tubule epithelium, which enhances sodium reabsorption and impairing aldosterone escape, perpetuating vol-
ume overload with the potential for cardiac dilatation, left ventricular hypertrophy, and blunting beneficial arterial-reflex responses. The resulting volume overload in CHF patients is most frequently treated with loop diuretics, which block sodium chloride transport via the macula densa, resulting in further activation of the RAAS (Schrier RW. Nat Clin Pract Nephrol 2007; 3:637).

The heart in renal dysfunction
A body of observational population stud-
ies have indicated that CKD (defined as an estimated GFR of <60 mL/min/1.73 m²) due to a variety of systemic and kid-
ney-specific diseases is a strong and inde-
pendent risk factor for the development of coronary artery disease and cardiovascular disease mortality (Sarnak MJ, et al. Circula-
tion 2003; 108:2154). This is significant to an extent that the risk of cardiovascular death in CKD patients is much higher than the risk of eventually requiring renal replacement therapy. Besides CKD itself, a multitude of risk factors commonly ob-
erved in CKD patients contribute to the overall hazard of cardiovascular disease. These include volume expansion secondary to sodium retention and hypertension, diabetes, older age, and smoking history (Sarnak MJ, et al.).

CKD patients often have metabolic syndrome, which combines insulin resist-
ance, dyslipidemia, impaired glucose toler-
eance, abdominal obesity, and hyperten-
sion (Chrysant, et al. Am J Cardiol 1990; 140:167–74). Additional "nontraditional" risk factors are relatively unique to patients with advanced CKD. These include abnor-
malities in bone mineral metabolism with phosphate retention and increased par-
athyroid hormone concentration, inflam-
matory state, increased oxidized LDL cho-
lesterol, fibrinogen, and uric acid. These are cardiovascular risk factors that occur with CKD (Schrier RW, J Am Coll
Cardiol 2006; 47:1–8). Although some of these factors may only be markers of car-
diovascular disease, it is clear that some are pathogenetic factors for cardiovascular outcomes. Furthermore, rapidity of kid-

Dysfunction of the heart and the kid-
ney can simultaneously take place when a systemic disease affects both organs. Such dysfunction conceivably increases patient morbidity and mortality. Examples in-clude diabetes and hypertension, which can affect the heart by promoting coronary artery disease and CHF while concurrently affecting the microvasculature of the kid-
ney and precipitating renal dysfunction that may lead to sodium and water reten-
tion and cardiac consequences of volume overload.

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