The Chicken or the Egg

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beta-adrenergic stimulation and decreased sodium chloride delivery to the macula densa, both of which are expected events in CHF. Subsequently, angiotensin II causes myocardial remodeling and stimulates the sympathetic nervous system whereas aldosterone may increase myocardial fibrosis in the heart (Hirsch AT, et al. *Am J Cardiol* 1990; 66:22D–30D; Schrier RW et al. *Clin J Am Soc Nephrol* 2010; 6:1132–40).

Increased angiotensin and decreased nitric 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 vasoconstriction of the glomerular efferent arteriole by angiotensin II in CHF also alters net Starling forces in the peritubular capillary (decreased hydrostatic and increased oncotic pressure) in a direction to enhance sodium reabsorption. Thus, angiotensin and alpha-adrenergic stimulation increase sodium reabsorption in the proximal tubule by a direct effect on the proximal tubule epithelium and secondarily by renal vasoconstriction. Aldosterone increases sodium reabsorption in the collecting duct.

Activation of the RAAS in CHF may cause progression of cardiac dysfunction by: 1) direct myocardial effects of angiotensin and aldosterone causing cardiac remodeling and fibrosis, and 2) increasing proximal sodium reabsorption and impairing aldosterone escape, perpetuating volume overload with the potential for cardiac dilatation, left ventricular hypertrophy, and blunting beneficial atrial-renal reflexes. The resulting volume overload in CHF patients is most frequently treated with loop diuretics, which block sodium chloride transport at 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 studies have indicated that CKD (defined as an estimated GFR of <60 mL/min/1.73 m^2) due to a variety of systemic and kidney-specific diseases is a strong and independent risk factor for the development of coronary artery disease and cardiovascular disease mortality (Sarnak MJ, et al. *Circulation* 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 observed 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 resistance, dyslipidemia, impaired glucose tolerance, abdominal obesity, and hypertension (Chen J, et al. *Ann Intern Med* 2004; 140:167–74). Additional "nontraditional" risk factors are relatively unique to patients with advanced CKD. These include abnormalities in bone mineral metabolism with phosphate retention and increased parathyroid hormone concentration, inflammatory state, increased oxidative stress, anemia, left ventricular hypertrophy, and proteinuria, all of which could increase cardiovascular disease (Figure 2).

Albuminuria has clearly been shown to be not only a risk factor for progression of CKD but also a risk factor for cardiovascular mortality. Increased plasma homocysteine, fibrinogen, and uric acid are other 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 cardiovascular disease, it is clear that some are pathogenetic factors for cardiovascular outcomes. Furthermore, rapidity of kidney function decline was correlated with cardiovascular risk in two recent studies that demonstrated poorer cardiovascular outcomes with rapid decline after multiple adjustments for other risk factors and baseline kidney function (Matsushita K, et al. *J Am Soc Nephrol* 2009; 20:2617–24; Shlipak MG, et al. *J Am Soc Nephrol* 2009; 20:2625–30).

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

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Classification and Pathophysiology of Cardiorenal Syndrome

By Saurabh Goel, MD, Keith Bellovich, DO, and Peter McCullough, MD

Cardiac and renal diseases are common and frequently coexist, adding to the complexity and costs of care, and ultimately, to increased morbidity and mortality (1). A consensus conference on cardiorenal syndromes (CRS) was organized under the auspices of the Acute Dialysis Quality Initiative (ADQI) in Venice, Italy, in September 2008 to develop a classification scheme to define critical aspects of CRS.

After three days of deliberation among 32 attendees, summary statements were developed, defining CRS as disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other. The plural form indicates the presence of multiple subtypes of the syndrome and recognizes the bidirectional nature of the various syndromes. The subtypes recognize the primary organ of dysfunction (cardiac versus renal) in terms of importance and by temporal sequence and timeframe (acute versus chronic).

A structural and/or functional abnormality of both organs is necessary, and an additional subtype is added to capture systemic conditions affecting both organs simultaneously. The goal of this definition is to facilitate epidemiological studies, identify target populations for intervention, develop diagnostic tools, and prevent and manage different syndromes.

Five subtypes of CRS have been proposed. Their pathophysiological mechanisms are described in Figure 1. The ADQI working group recognized that many patients may populate or move among subtypes during the course of their disease, and this classification is not meant to pigeonhole a patient into a single category (Figure 2).

Acute cardiorenal syndrome (type 1)

Acute worsening of heart function leading to kidney injury and/or dysfunction

This is a syndrome of worsening renal function (WRF) as a complication of acute heart failure and/or acute coronary syndrome (ACS). Between 27 and 40 percent of patients hospitalized for acute decompensated heart failure appear to develop acute kidney injury (AKI) (1), which generally occurs early after presentation to the hospital. These patients experience higher mortality and morbidity and increased length of hospitalization.

In acute decompensated heart failure, the effects of vasoconstricting and sodium-retaining neurohormones such as angiotensin II, norepinephrine, endothelin, adenosine, and arginine vasopressin are counterbalanced by vasodilatory and natriuretic hormones such as natriuretic peptides, prostaglandins, bradykinin, and nitric oxide. The imbalance between the vasoconstriction/sodium retention and vasodilatation/natriuresis in favor of the former is pivotal in CRS and in sodium retention in these patients (4). Increased cardiac preload is associated with renal venous congestion, which is an important hemodynamic factor driving AKI in patients with acute decompensated heart failure (5).

In patients admitted to the intensive care unit with acute decompensated heart failure, AKI is associated with greater central venous pressure (CVP) on admission and after intensive medical therapy. This finding is consistent after adjusting for systemic blood pressure, pulmonary capillary wedge pressure, cardiac index, and estimated glomerular filtration rate (GFR) (5). Elevated adenosine levels in acute heart failure decrease GFR by vasodilatation of efferent capillaries, vasoconstriction of afferent capillaries, and by activating tubuloglomerular feedback. This creates the appearance of pre-renal azotemia in a patient who is clearly volume overloaded. The use of iodinated radiocontrast agents, nonsteroidal anti-inflammatory agents, and other nephrotoxic drugs can further exacerbate renal dysfunction. Vasodilators and loop diuretics widely used in treatment of acute decompensated heart failure can also contribute to reductions in GFR, and in some cases, may be the direct precipitants of CRS.

Chronic cardiorenal syndrome (type 2)

Chronic abnormalities in heart function leading to kidney injury and/or dysfunction

This subtype refers to a more chronic state of kidney disease complicating chronic heart disease. Chronic cardiorenal syndrome is common and has been reported in 63 percent of patients hospitalized with heart failure (6). Chronic kidney disease (CKD) is associated with higher all-cause and cardiac-specific mortality (6). A "dose-response" or graded association between decline in GFR

and worsening clinical outcome is generally noted.

An example of type 2 CRS is chronic heart failure, where chronic cardiac dysfunction can result in adaptive alterations in kidney perfusion and neurohormonal activation. In a study of 1102 adult patients with heart failure, over 50 percent had evidence of kidney dysfunction. Nine percent had GFR <60 mL/min/1.73 m^2, and this was associated with a threefold increase in mortality (7). It is recognized that patients may transition between type 1 and type 2 CRS at various stages in their disease.

Initiation of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) may cause a mild increase in serum creatinine but does not contribute to CRS. Other causes contributing to real decline of renal function include excessive diuresis, persistent hypotension, prescriptions for nephrotoxic agents, vasodilators, and underlying renovascular disease. Anemia is a common finding in patients with type 2 CRS as a result of relative or absolute erythropoietin deficiency combined with a functional decrease in iron utilization as a result of increased hepcidin levels, which block iron transfer to hematoblasts. Correction of the anemia may improve symptoms but has not been shown to reduce clinical endpoints or mortality.

Acute renocardiac syndrome (type 3)

Acute worsening of kidney function leading to heart injury and/or dysfunction

This subtype refers to abnormalities in cardiac function secondary to AKI. The pathophysiologic mechanisms contributing to acute dysfunction of the heart likely go beyond simple volume overload to include uremic changes, electrolyte derangements, humoral mediators, and mediators of inflammation. Untreated uremia depresses myocardial contractility and contributes to pericardial inflammation. Hyperkalemia can precipitate arrhythmias and cardiac arrest, while acidemia results in negative inotropic effects and an increased risk of arrhythmias. Renal ischemia itself may precipitate activation of systemic oxidative stress leading to apoptosis of cardiomyocytes.

An example of type 3 CRS is the development of an ACS, arrhythmia, or acute decompensated heart failure after the onset of AKI such as acute glomerulonephritis or acute tubular necrosis. Another common scenario is cardiac surgery-associated AKI (CSA-AKI) with a reported incidence between 0.3 and 29.7 percent (8). In this condition, AKI contributes to fluid overload and worsened left ventricular pump mechanics. It is appreciated that CSA-AKI may also represent type 1 CRS.

Some patients with contrast-induced AKI develop progressive renal failure, volume overload, and acute decompensated heart failure requiring intensive care treatment and/or transient and sometimes permanent dialysis (9). Solomon et al. (10) showed that patients with contrast-induced acute kidney injury were almost twice as likely to suffer subsequent adverse cardiovascular events in the year following the contrast exposure, indicative of the serious consequences of type 3 CRS.

Chronic renocardiac syndrome (type 4)

Chronic kidney disease leading to heart injury, disease, and/or dysfunction

This subtype refers to disease or dysfunction of the heart that occurs secondary to CKD. Cardiac disease in CKD patients is common, and cardiac-specific mortality rates are ten- to 20-fold higher compared with age and sex-matched non-CKD populations (11). Several observational studies have found a graded increase in the prevalence of CVD and heart failure, along with a higher risk of subsequent cardiac events associated with the degree of decline in kidney function (12). This dose-response trend also translates into similar trends for the risk of cardiac-specific and all-cause mortality (12).

Type 4 CRS involves the progression of CKD, often due to diabetes mellitus and hypertension, with accelerated calcific atherosclerosis, anemia, progressive left ventricular hypertrophy, and the development of diastolic and systolic dysfunction. Sodium retention occurs in progressive CKD from reduced renal excretion, and in patients on hemodialysis due to dietary noncompliance, inappropriately high dialysate sodium, and the inability to achieve target or "dry" weight. The dialysis procedure itself has been implicated in chronic myocardial injury and the activation of multiple proteinases that could be destabilizing to atherosclerotic plaque. However, it has been observed that most of the cardiac mortality in dialysis patients is not attributed to coronary ischemia but is more consistent with pump failure or lethal arrhythmias as the terminal event.

Secondary cardiorenal syndrome (type 5)

Systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney

In secondary CRS, both organs are simultaneously affected by systemic illnesses, either acute or chronic. Examples include sepsis, systemic lupus erythematosus, diabetes mellitus, amyloidosis, or other chronic inflammatory conditions. Sepsis is common and its incidence is increasing, with an estimated mortality of 20–60 percent. Approximately 11–64 percent of septic patients develop AKI that is associated with a higher morbidity and mortality (13). Abnormalities in cardiac function are also common in sepsis.

Observational data have found that approximately 30–80 percent of septic patients have elevated cardiac-specific troponins that often correlate with reduced left ventricular function. Currently there is an incomplete understanding of the pathophysiologic mechanisms causing such changes, but they may involve the effect of tumor necrosis factor (TNF) and other inflammatory mediators on both organs (14,15). Systemic inflammation and cellular injury leads to the liberation of small quantities of labile iron from organelles, and this acts as the critical substrate for the generation of oxygen free radicals, which propagate tissue injury (16). Myocardial depression leading to decreased cardiac output can further deteriorate renal function. Renal ischemia may induce further myocardial injury. Treatment of the primary illness in general improves both heart and kidney function.

The classification of CRS presented will allow development of a clinical and research framework for improved recognition and treatment of CRS in the future.

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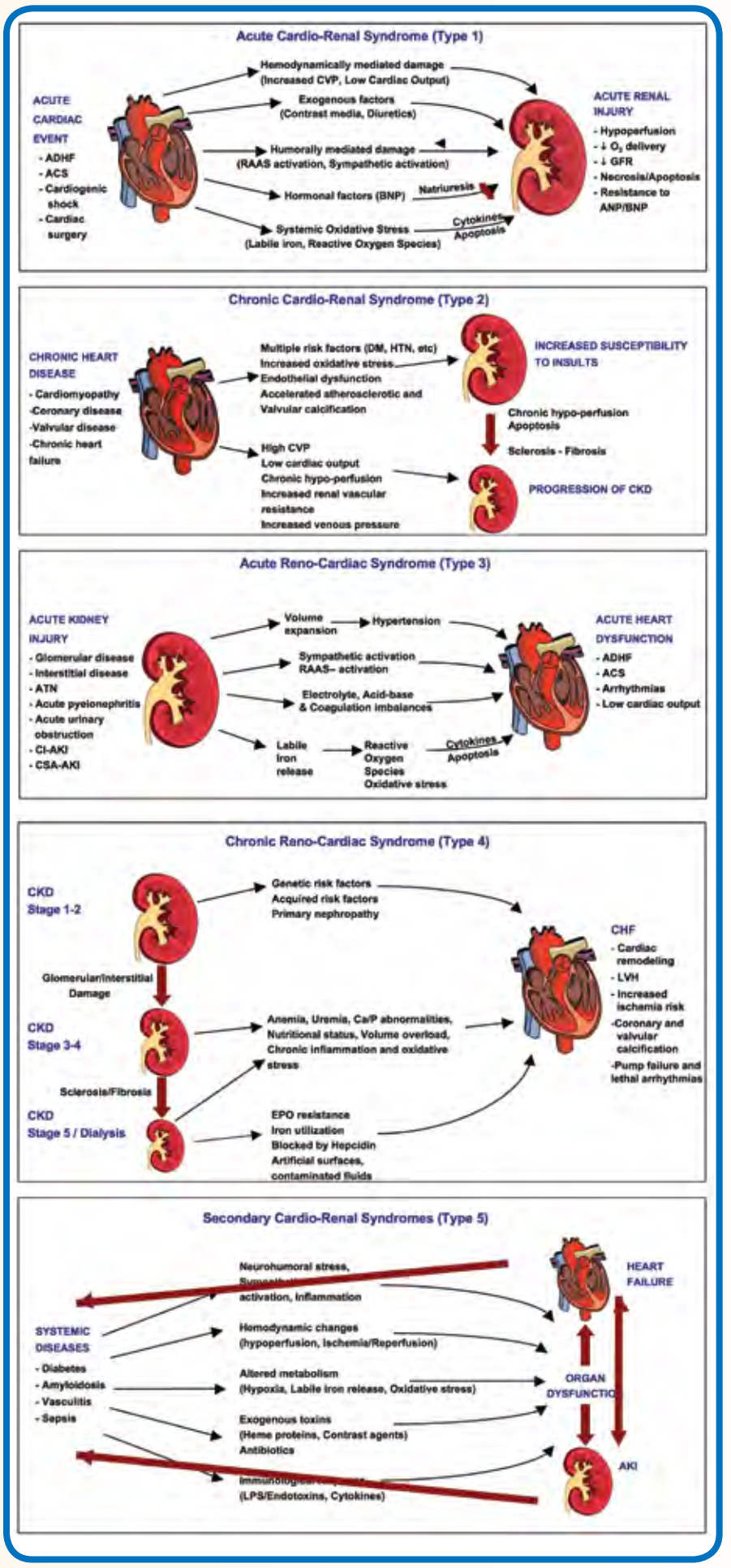
Figure 1

Classification and pathophysiology of the five subtypes of cardiorenal syndrome



Abbreviations: RAA = renin angiotensin aldosterone; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; ATN = acute tubular necrosis; EPO = erythropoietin. Modified from (2,3)

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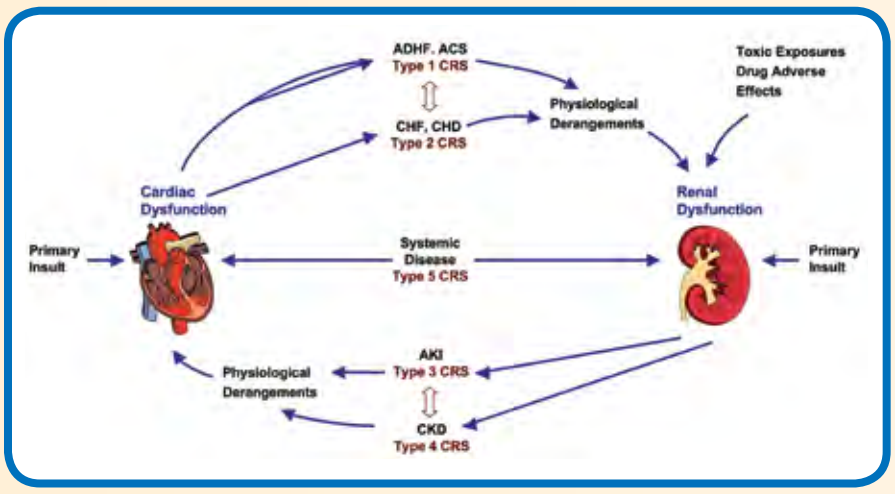
Figure 2
Heart-kidney interactions



Two important features characterize cardiorenal syndromes: the sequence of organ involvement and the bidirectionality of signaling, leading to a vicious cycle of cardiac and renal dysfunction. Another important aspect is the timeframe in which the derangements occur (chronic or acute). The series of conditions shown here indicate that patients may move among the subtypes of cardiorenal syndromes. Modified from (2).

Experimental models of cardiorenal syndrome: from basic science to the clinic

By Susana Pérez, Alejandro Bernasconi, Carlos Musso, and Jordi Bover

The interaction between the heart and the kidney is well known. Congestive cardiac failure can be tied to acute renal failure with prerenal origin or, if it is sustained in time, to renal failure. Chronic cardiac disease and chronic kidney disease can both lead to chronic disturbances in the other organ. Lindner et al. published work describing the association between hemodialysis and accelerated atherosclerosis (1). Although the existing relationship between renal failure and cardiovascular risk has been overlooked until recently, it has now become one of the most important issues in nephrology (2–4). Five types of cardiorenal syndrome have recently been identified—from acute to chronic cardiac and renal conditions (5).

The Acute Dialysis Quality Initiative (ADQI) consensus conference elaborated an executive summary of these cardiorenal syndromes (5). In 1998, a group of experts from the National Kidney Foundation reported an important increase in mortality among patients undergoing dialysis compared with the general population (6). For this reason, different groups of experts recommend that patients with chronic kidney disease (CKD) be considered at high risk for cardiovascular disease (ECV) (6).

Sarnak et al. reported that not only is ECV associated with CKD but also that in patients with CKD the mortality with associated ECV is increased in relation to their base renal pathology (7). This relatively high mortality risk increased several hundredfold compared with the mortality of young patients in the general population and patients of the same age in a hemodialysis program (8). The increase in detection of CKD combined to ECV is a new area of interest in epidemiology, especially in developed countries (7,8).

The definition of CKD (9,10) is important not only with regard to early detection, but also in its association to ECV risk. Therefore, the definition has been associated with renal alterations in the analysis of the patient's cardiovascular risk (11,12). Compared with the general population, CKD patients have an increase in the prevalence of myocardial ischemic disease, left ventricular hypertrophy, and congestive cardiac failure (10,11). In patients on hemodialysis or peritoneal dialysis, the prevalence of heart disease is approximately 40 percent and 75 percent, respectively, with an annual cardiovascular mortality rate of 4–5 percent. Also well known is the relation between calcification and several nontraditional risk factors (e.g., vitamin D status, activation of the renin-angiotensin-system and cardiovascular risk in CKD) (13,14).

Development of an experimental animal model to study the physiology of the cardiorenal axis and to assess and develop new therapeutics is needed. This review focuses on the major animal models currently used to investigate the cardiorenal axis.

Experimental models

We reviewed four experimental models that analyze the cardiorenal axis in wild type animals and three models of genetically modified (knockout) animals. In a study by Dikow et al., partially nephrectomized rats' left coronary arteries were ligated for 60 min, followed by reperfusion for 90 min. The researchers measured the nonperfused risk area (total infarction plus penumbra) and the area of total myocardial infarction (MI). They found that a greater proportion of nonperfused myocardium undergoes total necrosis, which is consistent with the hypothesis of reduced ischemic tolerance of the heart in renal failure, independent of hypertension, sympathetic activation, or salt retention, and that these findings could explain the high rate of death from MI in patients with impaired renal function (16).

Van Dokkum et al. studied the effects of MI on mild renal function loss in unilateral nephrectomized rats with sham animals as controls. The rats were separated into two groups according to MI size; less than 20 percent was considered a small MI and greater than 20 percent a moderate MI. There were no animals with MI over 40 percent. In the first experimental group, proteinuria was 55.5 mg/day. In the second group, it was 124.5 mg/day, demonstrating how renal injury due to MI was accelerated. Left ventricular pressure correlated with proteinuria (16). On the other hand, it is clear that microalbuminuria is an independent cardiovascular risk factor, even in the range considered appropriate. Microalbuminuria is a window from the kidney to the vascular system and reflects more than the renal disease; it can reflect generalized endothelial dysfunction or the beginning of vascular remodeling (17).

Van Dokkum et al. also looked at an experimental model of renal damage induced