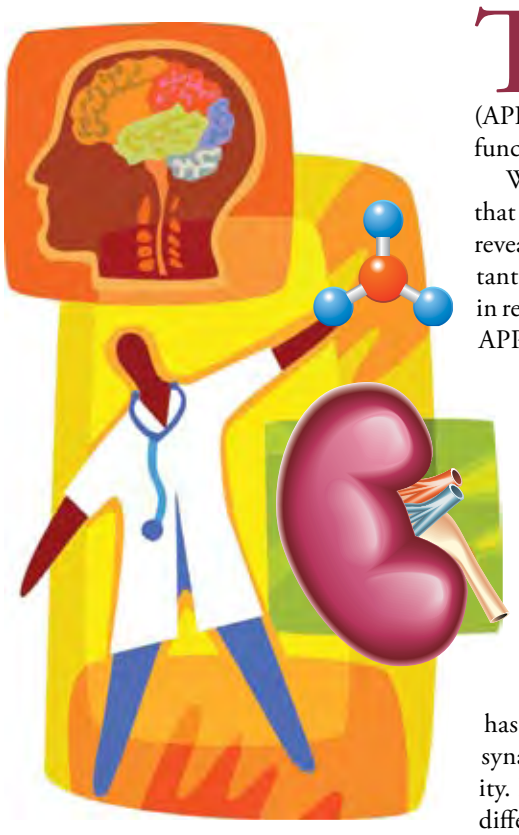
ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Kidney News

September 2010 | Vol. 2, Number 9

Alzheimer's and Kidney Disease: Common Molecular Culprit?

By Cathy Yarbrough



The suspected molecular villain in Alzheimer's disease (AD)—the amyloid precursor protein (APP)—may also play a role in kidney function, new research finds.

While the findings do not suggest that APP "causes" kidney disease, they reveal that this protein may play important, although poorly understood, roles in renal function. Continued research on APP may help unravel kidney disease's complex mechanisms and prompt researchers developing drugs targeted for the treatment of AD to also examine the compounds' effects on patients' kidneys.

Thus far, APP's complexity has defied numerous attempts by scientists to define how it might cause AD. In studies of brain tissue from AD patients and in animal models of the disease, APP has been implicated as a regulator of synapse formation and neural plasticity. Its expression is upregulated during differentiation and neuronal cell injury.

"We've known about APP since the late 1980s, but we've not yet determined APP's role in the brain, much less other body organs and tissues," said Lorenzo Refolo, PhD, a neuroscientist specializing in APP's molecular and cell biology at the National Institute on Aging.

That said, APP is highly expressed throughout the kidney, said Daniel Biemesderfer, PhD, of Yale University School of Medicine. Biemesderfer's lab has found that mice whose APP amyloid precursor–like protein-2 (APLP) genes were inactivated had a reduced glomerular filtration rate, lower urine osmolarity, and poorly developed renin granules in the juxtaglomerular cells.

"The distinct renal phenotype of the APP-/- mice suggests an important but not understood role in renal physiology," Biemesderfer said.

Thomas Willnow, PhD, of the Max-Delbrueck-Center for Molecular Medicine in Berlin, traced the APP kidney connection to a unique protein— SorLA

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Gene Variants that Protect Against Parasitic Disease Increase Kidney Disease Risk

By Tracy Hampton

Certain genetic variants found in more than 30 percent of African Americans may be considered a double-edged sword: a new study indicates that they protect against a parasitic infection but increase the risk of developing kidney disease (Genovese G, et al. Association of trypanolytic spoL1 variants with kidney disease in African-Americans. *Science.* doi: 10.1126/science.1193032 [published online ahead of print July 15, 2010]).

"The findings are very exciting," said Thomas Hostetter, MD, chief of the division of nephrology at the Albert Einstein College of Medicine. "Large risks from single genes seem rare for common diseases."

Studying how these genetic alterations contribute to kidney injury could help clinicians understand and potentially prevent kidney disease in individuals of recent African ancestry.

The good and the bad

The scenario may sound familiar—researchers have known for years that people with the hereditary blood disease sickle-cell anemia are protected against getting malaria. This is due to a muta-

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Inside

JAMES D.
Age: 56
Time on dialysis: 6 mo.
Lateral abdominal

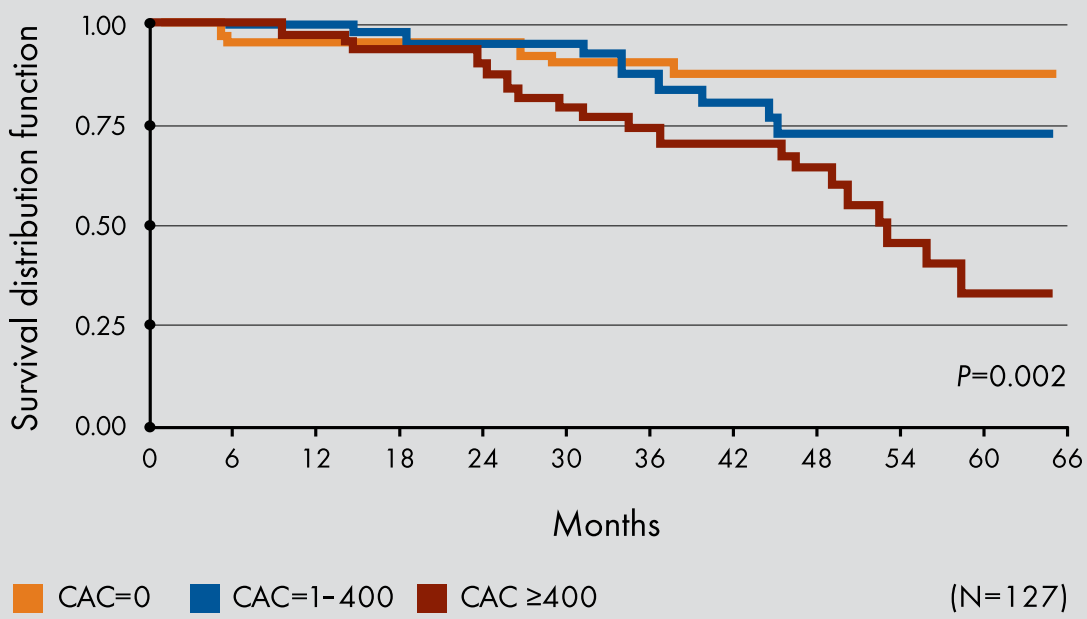
Ca^{+2}ution

64% of new dialysis patients[1] and 83% of prevalent dialysis patients[2] have been shown to have calcification.

2009 KDIGO guidelines[3] for CKD-MBD state:

The presence and severity of cardiovascular calcification strongly predict cardiovascular morbidity and mortality in patients with CKD.

A study by Block *et al* evaluated adjusted survival by baseline coronary artery calcification (CAC) score[4]*



*Multivariable adjusted (age, race, gender, diabetes).
P value represents significance across all 3 groups.

KDIGO suggests restricting calcium dose in the presence of[3]:

- **Persistent/ recurrent hypercalcemia†**
- **Arterial calcification**
- **Persistently low PTH levels**
- **Adynamic bone disease**

†KDIGO recommendation.

References: **1.** Spiegel DM, Raggi P, Mehta R, et al. Coronary and aortic calcifications in patients new to dialysis. *Hemodialysis Int.* 2004;8:265-272. **2.** Raggi P, Boulay A, Chasan-Taber S, et al. Cardiac calcification in adult hemodialysis patients: a link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol.* 2002;39:695-701. **3.** Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). *Kidney Int.* 2009;76(suppl 113):S1-S130. **4.** Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int.* 2007;71:438-441.

genzyme
Renal

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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Gene Variants

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tion in a hemoglobin gene found in red blood cells that causes the cells to take on a sickle shape. These sickled cells are not conducive to harboring malaria parasites, which live inside red blood cells. Unfortunately, individuals with two gene copies of the mutation have full sickle-cell disease and in traditional societies rarely live beyond adolescence. People with only one gene copy may have only a low level of anemia, but they benefit from a greatly reduced chance of serious malaria infection.

This latest research offers another example of how natural selection can favor harmful mutations if they also confer some form of benefit. Here, the gene involved is called APOL1, which is found on chromosome 22 and encodes apolipoprotein L-1. Apolipoprotein L-1 derived from genetic variants found in many African Americans—but not those found in Europeans and other groups—kills *Trypanosoma brucei rhodesiense*, a trypanosome parasite that causes African sleeping sickness.

"One variant copy of the *APOL1* gene seems to confer resistance to infection, but two copies are needed to increase risk of kidney disease," said principal investigator Martin Pollak, MD, of Beth Israel Deaconess Medical Center and Harvard Medical School in Boston.

To come to that conclusion, Pollak and his collaborators scoured data from the 1000 Genomes Projects—which is sequencing DNA of individuals from around the globe—to uncover two alterations (G1 and G2) in the *APOL1* gene that are associated with hypertension-attributed end stage kidney disease as well as focal segmental glomerulosclerosis, which involves the buildup of scar tissue in parts of the kidney. Comparing individuals with zero or one variant to those with two variants, the investigators found that people with two variants were 10.5 times more likely to have focal segmental glomerulosclerosis and 7.5 times more likely to have end stage kidney disease.

The investigators also assessed the potential link between *APOL1* gene variants and kidney disease in 1030 African American cases with hypertension-attributed end stage kidney disease and 1025 geographically matched African American controls from the southeastern United States. The G1 variant was found in 52 percent of glomerulosclerosis patient chromosomes, compared with 18 percent of control subject chromosomes. The G2 variant was approximately 50 percent more common in people with either form of kidney disease (end stage kidney disease or glomerulosclerosis) than it was in healthy people. Approximately 10 percent of individuals in the general African American population have two *APOL1* risk variants and are at increased risk for kidney disease.

The scientists also discovered that G1 was present in the chromosomes of many Yoruba people, who live in Nigeria, but not in any chromosomes from European, Japanese, or Chinese individuals. Similarly, G2 was detected in chromosomal sequence data from several Yoruba subjects, but not in the other three ancestral groups.

African sleeping sickness occurs only in sub-Saharan Africa in regions where there are tsetse flies that can transmit the disease, according to the World Health Organization. In affected individuals who do not receive treatment, the parasite invades the central nervous system, leading to confusion, sensory disturbances, poor coordination, disturbance of the sleep cycle (which gives the disease its name), and eventually death. While individuals in developed countries do not need protection against infection, at one point in history the *APOL1* gene variants seem to have provided an important survival advantage against African sleeping sickness to ensure their persistence through natural selection. This could explain their widespread prevalence today in modern cultures, where their positive effects no longer balance out their negative effects on the kidneys.

Clinical applications

These latest research findings may help explain why African Americans have higher rates of kidney disease than European-Americans, and they could improve our understanding of kidney disease by revealing key pathways involved in kidney injury. Much more work remains to fully understand how the *APOL1* variants play a role in injuring the kidneys.

"We need biologic and genetic studies to see what's going on with the *APOL1* variants and how they affect the kidneys," said Pollak. "This gene is present only in humans and certain other primates, so it's difficult to study in the lab." In addition, not everyone with two variants develops kidney disease, so additional studies are needed to determine what other factors are involved in affected individuals.

Further research is also needed to determine whether the findings might have diagnostic and therapeutic utility. "We need more clinical studies to see who should be screened and if they might be treated," said co-author Jeffrey Kopp, MD, of the National Institute of Diabetes, Digestive, and Kidney Disease, in Bethesda, MD. "If you test people with kidney disease and they are positive for the variants, what will you tell them to do differently? And would you treat them early, before any signs of kidney disease show up?" he asked.

Pollak noted that the research could help guide other gene discovery efforts. "We think this study might help in efforts that are looking for other genes that might have both beneficial roles, like resistance to infectious parasites, and detrimental roles, like increased risk of certain diseases," he said.

The work might also impact care for individuals in sub-Saharan Africa who develop African sleeping sickness. Perhaps man-made versions of altered apolipoprotein L-1, or even plasma from people who carry the G1 or G2 variants, could be effective new treatments.

Alzheimer's and Kidney Disease

Continued from page 1

(sorting protein-related receptor)—that is expressed in both neurons and renal cells and that regulates APP processing. Polymorphisms in the gene that encodes this receptor have been associated with late-onset AD. Willnow spoke during the 2009 ASN Renal Week symposium, "Kidney-Brain: Emerging Parallels in Cell Biology."

The kidney is not the only nonneural organ in which APP activity has been recently discovered. In papers published in 2008 and 2009, University of Vermont College of Medicine scientists reported that APP is highly expressed in adipose tissue and is upregulated in obesity. The researchers correlated APP expression levels with insulin resistance and adipocyte cytokine expression levels, suggesting a possible mechanism linking midlife obesity with the later development of AD.

The link between the kidney and brain is exemplified by the occurrence of drug toxicities that include the kidney and ear (in aminoglycosides, for example) and genetic syndromes that affect both organs, such as Bartter syndrome, with sensorineural deafness. Bartter syndrome is a genetic disorder accompanied by hypokalaemic metabolic alkalosis. The most severe phenotype for Bartter syndrome is characterized by life-threatening neonatal volume depletion and chronic renal failure developing during infancy.

The brain-kidney link is also illustrated by the name given to a scaffolding protein identified in 2002 by scientists at the University of Münster in Germany. Expression of mRNA for the protein, named KIBRA (kidney and brain), was detected in both organs, according to the scientists' paper, "Characterization of KIBRA, a novel WW domain-containing protein," published in *Biochemical and Biophysical Research Communications.*

These and other studies have revealed that KIBRA is expressed in the glomeruli, tubules, and collecting duct, as well as in the brain's memory-related regions including the hippocampus and cortex.

The University of Munster's Hermann Pavenstädt, PhD, reported in a 2008 paper in *Journal of the American Society of Nephrology* that directional cell migration is disturbed when KIBRA expression is reduced. In addition, Pavenstädt and his colleagues found that KIBRA directly interacted with synaptopodin, a podocyte protein that plays a role as cytoskeletal organizer and that is also associated with synaptic plasticity in neurons.

In the brain, KIBRA represents a component of the postsynaptic density, the researchers said. "Thus, our data support the hypothesis that the motility of podocyte foot processes and the flexibility of synaptic contacts of neurons could be regulated by an analogous set of molecules, including proteins such as KIBRA, synaptopodin, dendrin, actin, and actinin."

Because foot processes and dendrites are long F-actin–rich cellular extensions, KIBRA may play a role in the continuous regeneration and plasticity of both cell types.

The kidney-brain connection is a "real hot spot" in research, said Sebastian Bachmann, PhD, professor and chairman of anatomy and cell biology at the Humboldt University in Berlin.

"Leading papers from world class scientific groups are currently focusing on this issue and find substantial material that proves it is worthwhile to concentrate on common mechanisms in kidney and brain," Bachmann said. "This is well exemplified with APP and SorLA in both organs."

Since its discovery, most research on APP has targeted the brain and has led to the "amyloid hypothesis," which proposes that flaws in the production, accumulation, or disposal of β-amyloid, an APP microscopic protein fragment, somehow trigger Alzheimer's, perhaps by clogging points of cell-to-cell communication, thus activating immune cells that trigger inflammation and devour disabled cells.

Although APP's normal function has not yet been defined, scientists have discovered that in its complete form, APP extends from the inside to the outside of brain cells by passing through a fatty membrane around the cell. When APP is activated to do its normal job, it is cut by other proteins into smaller sections that stay inside and outside cells. One of the sections, β-amyloid, is chemically "stickier" than other APP fragments and accumulates by stages into microscopic amyloid plaques that are considered a hallmark of brains affected by Alzheimer's.

According to the Alzheimer's Association, several experimental drugs targeting β-amyloid have reached human clinical trials, but more time and studies are required before these compounds' effects on Alzheimer's symptoms or on brain cells can be clearly determined.

The results of Willnow's studies at the Max-Delbrueck-Center for Molecular Medicine indicate that low levels of SorLA are a primary cause of accelerated production of amyloid β-peptide, the principal component of senile plaques, and of senile plaque formation. Willnow's lab has shown that SorLA regulates intracellullar transport and processing of APP. Indeed, his lab also has found that high levels of SorLA expression reduce—and low levels of SorLA promote—senile plaque formation. Thus, altered SorLA activity may be an important risk factor for AD, according to Willnow.

Willnow hypothesizes that in the kidney, SorLA controls trafficking and activity of SPAK, an enzyme that regulates the cellular stress response and is part of a signaling pathway that regulates salt transport and blood pressure.

In kidney cells, SorLA also may influence the intracellular trafficking of shuttling compartments that contain the protein aquaporin2 (AQP2), regarded as "the plumbing system for cells." AQP2s are located in the apical cell membranes of the kidney's collecting duct and in intracellular vesicles located throughout the cell.

SorLA is mainly localized in the cell's Golgi apparatus, where it interacts with target proteins such as APP. Willnow has demonstrated that the Golgi's premature release of APP due to low SorLA activity subjects APP to accelerated proteoltyic cleavage into amyloid peptides. These results may explain how AD pathology is affected by the activity of the sorting receptor SorLA in the brain.

Willnow's lab has not yet investigated APP in the kidney. "Our main interest is the functional characterization of SorLA in the kidney," he said. "Of course, we will also explore whether the activity of the receptor in the kidney may include control of APP processing in renal cell types and what the physiological relevance of APP and its processing products may have in the kidney."

Findings from the Biemesderfer lab indicate the presence of what appears to be previously unknown signaling pathways in the kidney that involve APP and APLP.

Biemesderfer and his colleagues became interested in APP after discovering that the proximal tubule scavenger receptor megalin is subjected to regulated intramembrane proteolysis (RIP). Suspecting that RIP's relationship with megalin may represent part of a signaling pathway linking events at the brush border with regulation of target gene expression, the lab conducted research that led to the identification of ADAM10 as a proximal tubule protease. The ADAM10 findings suggested that the proximal tubule has other receptors that are subjected to RIP.

"From some old literature we noticed that there are large amounts of APP and APLP2 mRNA in kidney," said Biemesderfer. Based on this information, his lab initiated the studies that found high levels of APP and APLP2 in adult mouse kidney and in several proximal tubule cell lines. The lab then identified where renal APP is expressed along the nephron. They localized APP at the cellular and subcellular levels in mouse kidney and described the renal phenotype of APP-/- mice, whose APP and APLP2 genes have been inactivated.

"Our data suggest that these proteins are involved in signaling pathways in proximal tubule that may regulate gene expression," Biemesderfer said.

In other work, Rong Cong, PhD, and colleagues in Biemesderfer's lab reported that the protease ADAM10 and APLP2 are expressed in cultured proximal tubule cells. They also reported that ADAM10 activity has a pronounced effect on expression of specific proteins of the renal brush border.

Biemesderfer's lab continues to investigate APP in the kidney. "Our goal is to understand how APP and APLP2 function in kidney and especially in the proximal tubule," he said. "Based on gene knockout studies in brain, it is thought that APP and APLP2 serve redundant functions. Therefore, our next study will use mouse genetics to knock out both genes in proximal tubule. We predict a phenotype that will give us important clues as to the function of these proteins in this part of the nephron."

ASN News

ASN Launches Facebook Group

Facebook is not just for college kids anymore. It is the fifth most popular website in the world and reaches over 500 million users on a monthly basis. With projections of phenomenal growth in the future, Facebook and other social media sites represent a shift in how people discover, read, and share news, information, and content.

ASN serves an important community of people interested in improving kidney health. The society extends its support of this community by using Face book to convey information of interest to members and, most importantly, receive feedback from members.

ASN's Facebook page is a forum for participants to stay informed about advocacy and public policy, educational opportunities, breaking news, plans for ASN Renal Week, current research, grant funding and ASN services. We hope this venue helps members connect with each other, facilitates discussion and sharing of information, and provides key feedback to the society so that ASN may continue to improve services to members.

ASN members and medical students can join the ASN Facebook group through a link on the ASN website homepage (www.asn-online.org) or by searching for the group on Facebook. (Please note that there is a difference between the ASN fan page and the ASN group. The Society is not affiliated with the fan page.)

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

The Kidney Cardiac Link

ASN Kidney News *thanks editorial board member Edgar Lerma, MD, of the University of Illinois at Chicago College of Medicine for editing this special issue.*

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 pathophysiological 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.

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 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.

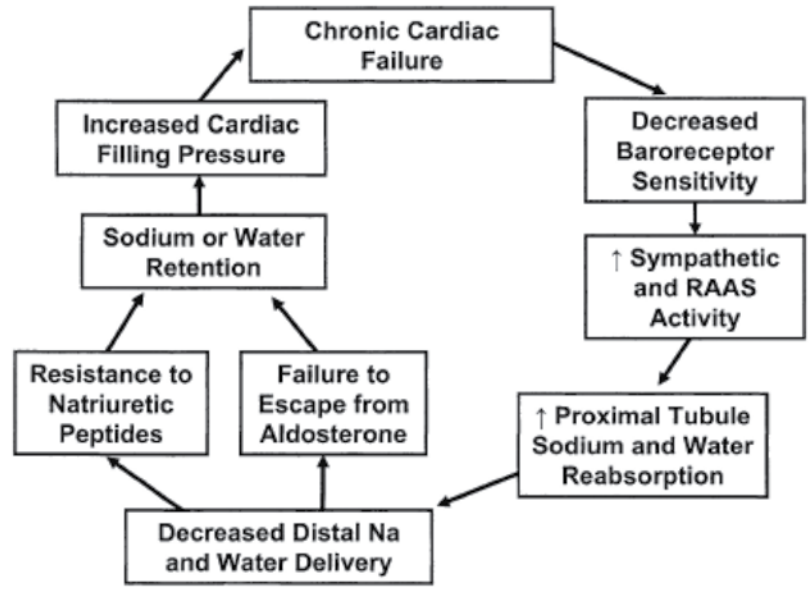
The primary function of the kidney is to regulate extracellular fluid volume (ECF) homeostasis. Slight deterioration of kidney function impairs the ability to maintain ECF volume and results in salt and water retention that subsequently leads to ECF volume expansion. ECF volume expansion can increase 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 cardiac 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

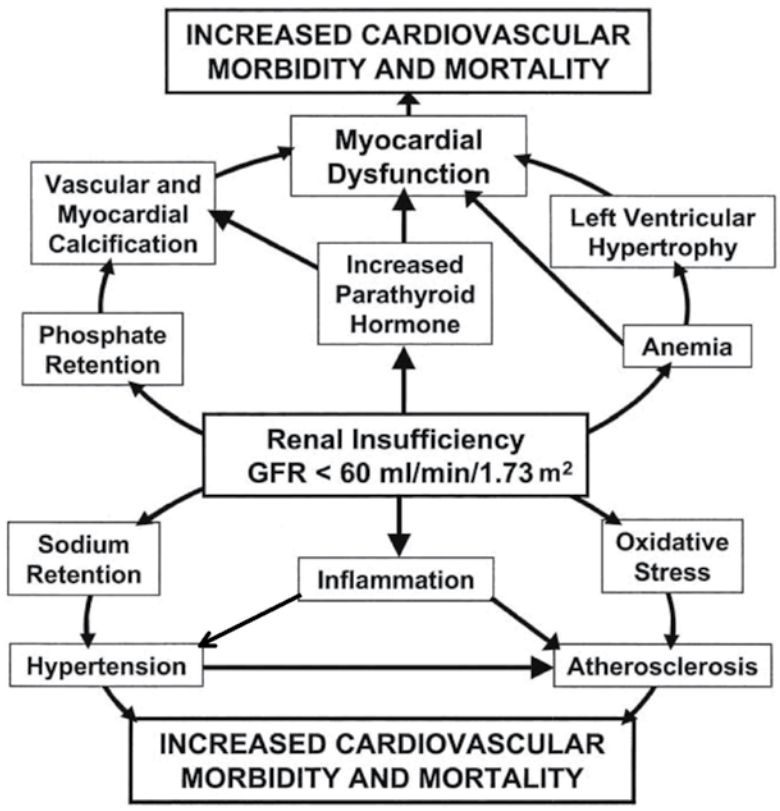
Continued on page 8

Figure 1



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).

Figure 2



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

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.

Elwaleed Elhassan, MD, is a renal fellow and Robert Schrier, MD, is professor in the department of medicine, division of renal diseases and hypertension, at the University of Colorado-Denver in Aurora, CO.

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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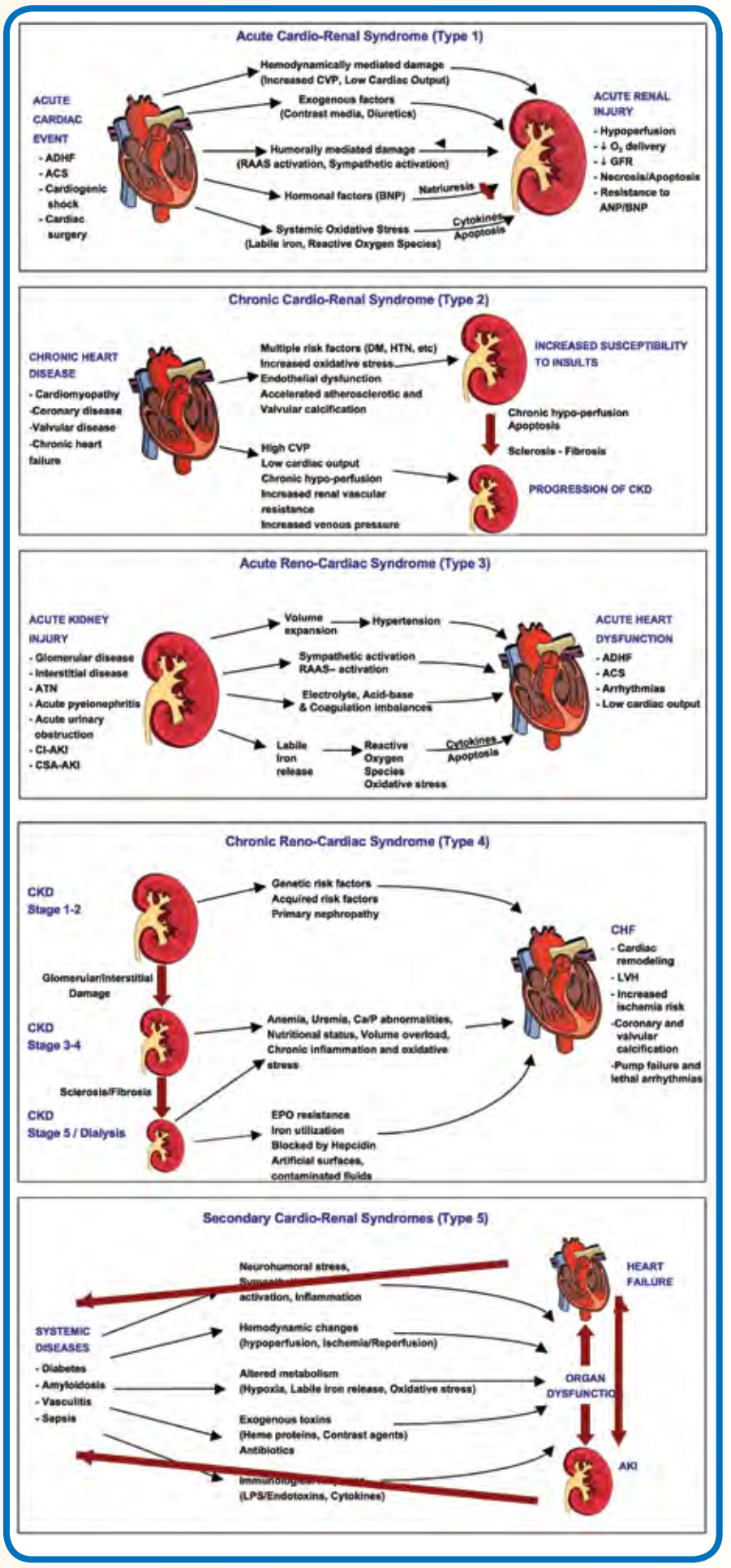
Continued on page 10

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)

Classification and Pathophysiology

Continued from page 9

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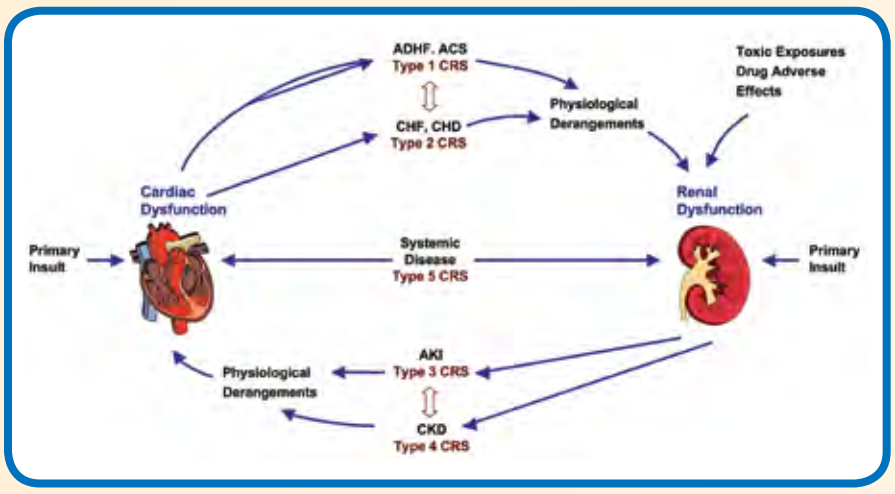
Figure 2
Heart-kidney interactions



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

by 5/6 nephrectomy plus a ligature of the coronary artery a week after surgery. They evaluated endothelium-dependent relaxation to acetylcholine in vitro in small arteries isolated from the extirpated 5/6 nephrectomy. After the MI, the nephrectomized rats gradually developed proteinuria in a range varying from 20 to 507 mg/day at week 16, with an average systolic blood preassure of 131±7 mm Hg. They found that individual renal endothelial function of the healthy rats predicted the extent of renal damage in terms of proteinuria ($r = -0.62$, $p = 0.008$) and focal glomerulosclerosis ($r = -0.70$, $p = 0.003$) (18).

Fedulov et al. studied serum levels of TGFβ1 and TNFβ in rats with cardiac fibrosis during chronic renal failure. They performed a unilateral nephrectomy and electrocoagulation of 25 percent of the cortex of the remnant kidney. The cardiac collagen correlated with both serum TGFβ1 levels and time from onset of follow-up at two, four, and six months (19). Finally, Wong et al. evaluated whether mild and severe renal failure shortens cardiac telomeres and excessively shortens telomeres after MI in rats subjected to sham, unilateral, or 5/6 nephrectomy to induce no, mild, or severe renal failure, and left coronary artery ligature to induce MI. They concluded that severe renal failure, but not mild renal failure, leads to shortening of cardiac telomeres to a similar extent as found after MI, and that renal failure did not induce excessive telomere shortening after MI (20).

Brymora et al. assessed the systemic inflammatory response (defined as the seric haptoglobin level), local inflammation (through use of monocytes chemoattractant protein MCP-1 levels), and the arterial response to phenilephrine in different stages of renal failure. For this purpose they performed a nephrectomy in rats divided into four groups: control, half nephrectomy, 3/5 nephrectomy, and 5/6 nephrectomy. The investigators found a lower arterial contraction in the 5/6 nephrectomized group. Systemic inflammation was evident in the half nephrectomized group with no evidence in the advanced stages of renal desease. Local inflammation increased progressively with renal failure.

It is clear that inflammation affects smooth muscle cells of the vessels and plays a key role in the final vascular tone (21). We proposed a rat model in three stages: First we perfomed a 5/6 nephrectomy in the left kidney; a week later, nephrectomy of the contralateral kidney; and finally, a ligature of the coronary artery to achieve mild MI. Sham controls in each group underwent the same technique as treated rats. It would be interesting to study the cardiorenal axis with different levels of renal insufficiency and with and without myocardial infarction (22,23).

There are three transgenic models in mice: knockout (KO) apolipoprotein E (APOE-/-) mice with accelerated atherosclerosis in uremia (24), KO mice for the LDL receptor (LDL-/-) (25), and AT1 KO mice (26).

In the first two models, APOE-/- and LDL-/-, hyperphosphatemia and vascular calcification was found, and animals with chronic renal disease had a worse prognosis. Those treated with bone morphogenetic protein-7 (BMP-7) in the LDL model improved (25).

The third model of Li et al. assessed the molecular pathway mediated by AT1A in cardiac dysfunction and renal dysfunction. They used wild mice and AT1 KO mice. In both cases they performed a 5/6 nephrectomy. The observed effects in the wild group (hypertrophy, dilatation, fibrosis, and a reduction in the capillary density) were significantly less important in the AT1 KO group. The valsartan treatment in the wild type mice improved the cardiac function to a level as good as that in the AT1 KO group (26).

Increasing evidence links the kidney and the heart through different humoral stimulus.This has not only been proven at an experimental level, but also in day-to-day clinical pratice. A better understanding of this tight relationship and consideration of the kidney and the heart as an axis will allow future development of drugs that can intervene in such an axis in an integrated way, thus achieving a more rational therapeutics of the cardiorenal and renocardial conditions that affect thousands of patients worldwide. The goal of these experimental models is to find the underlying mechanism enabling improved protection for both kidneys and heart.

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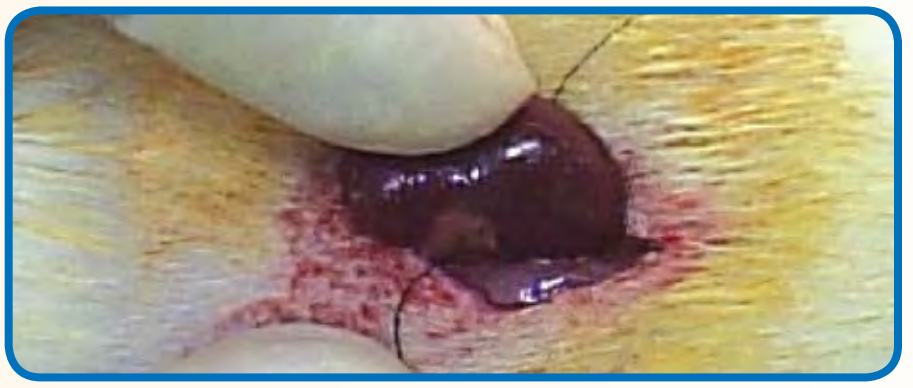
Figure 1. Technique of 5/6 nephrectomy in rat model: ligation of one branch of the renal artery

Figure 2. Technique of total nephrectomy contralateral to the 5/6 nephrectomy in rat model: complete ligation of renal artery and vein and escision of the kidney



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Cardiorenal Syndrome:
The Nephrologist's Perspective

By Domenic Sica

Renal dysfunction is a common and often progressive complication of heart failure (Figure 1). Renal function is—to use a descriptive term—"twitchy" in the patient with heart failure. It can change relating to patient volume status, concomitant medications, and adequacy of pump function, with all factors influenced by the background level of renal function. When corrective measures are taken in patients who experience a "bump" in serum creatinine levels, and renal function returns to baseline, all is well from a nephrologist's perspective—at least for the moment. Patients who experience transient deterioration in function would be viewed as having a moment of poor cardiac and renal crosstalk, but not necessarily cardiorenal syndrome (CRS).

A recent classification of CRS into categories, although arbitrary, provides needed perspective for the nephrologist on the sorting of the sometimes puzzling bidirectional nature of kidney–heart interactions (Figure 1). Five subtypes of CRS have been proposed that reflect the temporal nature of organ interactions as well as the primary and secondary pathology of kidney-heart crosstalk.

Type 1 CRS (acute cardiorenal syndrome) is an abrupt worsening of cardiac function, such as acute decompensated heart failure, leading to acute kidney injury. Type 2 CRS (chronic cardiorenal syndrome) comprises chronic abnormalities in cardiac function, such as chronic advanced stage heart failure causing progressive and permanent chronic kidney disease. Type 3 CRS (acute renocardiac syndrome) is an abrupt worsening of renal function, such as nephrotic syndrome, provoking an acute cardiac disorder, such as heart failure or coronary ischemia. Type 4 CRS (chronic renocardiac syndrome) comprises chronic kidney disease of any origin contributing to structural and functional cardiac abnormalities and a heightened risk of cardiovascular events. Type 5 CRS (secondary cardiorenal syndrome) is a systemic condition, such as sepsis, causing both cardiac and renal dysfunction (1).

Nephrologists who treat patients with CRS should assume that cardiac function has been optimized with available medication and device therapies. If these corrective measures do not result in any meaningful improvement in renal function and electrolyte status, the nephrologist enters into the fray in a more defined way. Mindful of the diverse ways in which the kidney may be affected by cardiac dysfunction, the nephrologist should adopt a systematic treatment approach that optimizes diuretic therapy, corrects electrolyte abnormalities, stabilizes blood pressure, and manages anemia (Table 1). Of these treatment considerations, optimizing diuretic therapy and stabilizing renal function are by far the most important and are where the nephrologist best fits in.

Most patients with CRS are significantly volume overloaded and are typically viewed as being diuretic refractory or diuretic resistant (2). In heart failure patients who respond poorly to conventional doses of a loop diuretic, high-dose therapy may prove effective. In one study, daily doses of 500 to 2000 mg of intravenous furosemide were administered to a series of patients with heart failure and refractory edema. With this regimen, a diuretic response was elicited, body weight was reduced, and heart failure class was improved. Similar studies have reported improved furosemide efficacy in refractory heart failure when high doses of oral furosemide are administered (3). Administering a loop diuretic as an infusion, rather than as bolus therapy, is another treatment stratagy that can improve the diuretic response in the heart failure patient with diuretic resistance. A significantly greater diuresis/natriuresis is observed frequently when a continuous loop diuretic infusion is given compared with intermittent bolus administration; this differential benefit is accomplished at lower peak loop diuretic concentrations. When continuously infused, this method of loop diuretic delivery results in a more efficient delivery of the drug to its site of action in the nephron (4).

Diuretic combinations can also be used in heart failure patients who are otherwise refractory to loop diuretics alone. The process of combining diuretics that work at different nephron segments is called sequential nephron blockade. Because of structural adaptation occurring in the distal nephron with prolonged loop diuretic therapy, the combination of a distal-acting diuretic and a loop diuretic is particularly effective in such patients.

Numerous reports have demonstrated significant diuresis accompanied by clinical improvement with the addition of metolazone to a loop diuretic (usually furosemide) in heart failure patients previously resistant to loop diuretic therapy alone. Metolazone is particularly effective because its duration of action is quite prolonged, it is lipophilic with a large volume of distribution, and it remains effective in advanced stage renal failure (5). Spironolactone has also been used in combination with loop diuretics and thiazide-type diuretics and has improved the diuretic response in diuretic refractory heart failure patients; however, the risk of hyperkalemia is greater in the cardiorenal patient, and spironolactone should be given cautiously if at all.

Recent clinical studies of intravenous dopamine, natriuretic peptide infusion, or oral adenosine or vasopressin antagonists have all been ineffective in reliably improving the response to diuretic therapy in patients with evolving CRS. A final issue with volume control in the CRS patient is that of isolated ultrafiltration, which can be performed by a nephrologist in a dialysis unit setting (although this procedure has recently become commonplace in heart failure units in a nephrologist-independent manner).

The ultrafiltration device used in heart failure units is 0.12 m^2 and can be used with either peripheral or central access in that the required blood flow is 10 to 40 mL/min (total filter set volume of 33 mL). Up to 500 mL of isotonic fluid can be removed hourly, and the filters last for one to two days on average. Several recent clinical trials have demonstrated the safety and feasibility of ultrafiltration in the management of acute decompensated heart failure. Ultrafiltration may be more effective at removing fluid than standard diuretic therapy, and it has been associated with some beneficial long-term results (6). However, it remains to be determined whether ultrafiltration is truly nephroprotective, what its actual safety profile is, and what its real cost-effectiveness is. An additional issue with isolated ultrafiltration is the extent to which dialysis unit staff should provide support for non–dialysis unit procedures occurring elsewhere in the hospital.

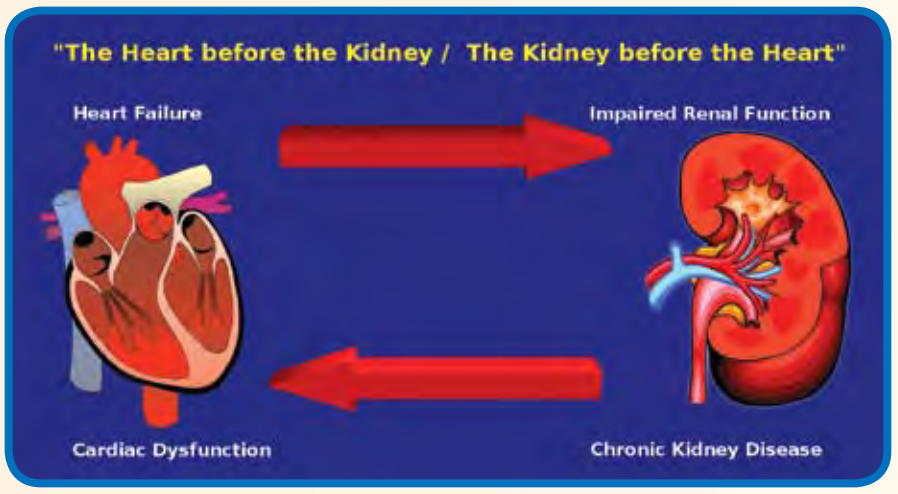
Because renal impairment in the setting of CRS is a very important indicator of adverse outcome, every effort should be made to prevent any significant (>25 percent of basal value) rise in serum creatinine levels consequent to diuretic unloading therapy. Unfortunately, this proves quite difficult, and diuretic therapy is often stopped because of the degree to which serum creatinine "bumps" with even modest unloading. Renal function can deteriorate suddenly when renin–angiotensin–aldosterone system inhibitor therapy is first begun. In addition, it can acutely change in patients receiving chronic therapy, particularly patients with systolic heart failure who have a low pretreatment mean arterial pressure value as well as some pre-existing level of renal failure.

In most patients who experience worsening renal function with renin–angiotensin–aldosterone system inhibitor therapy, one or more of three main mechanisms can be implicated (7). First and most importantly, if the mean arterial pressure falls to levels that are insufficient to sustain renal perfusion or that provoke substantial reflex renal sympathetic nerve activity, renal function will worsen. Angiotensin-converting enzyme inhibitor–related hypotension is generally more common with long-acting agents or in situations in which the pharmacologic half-life of an angiotensin-converting enzyme (ACE) inhibitor is inordinately prolonged, as occurs when the degree of renal insufficiency is underestimated and an ACE inhibitor cleared predominantly by renal pathways is given. Second, ACE inhibitors or angiotensin receptor blockers (ARBs) are more likely to cause acute kidney injury in the patient with heart failure

Table 1. Nephrologic considerations in patients with cardiorenal syndrome

1. Consultation for diuretic refractory patients with acute heart failure with need for bridging extracorporeal therapy
2. Management of prerenal azotemia when significant
3. Management of clinically significant hyperkalemia or hyponatremia
4. Consultation for appropriate drug dosing and drug interactions in renal insufficiency
5. Management of severe hypertension and pulmonary edema associated with diastolic dysfunction
6. Management of acute heart failure in anuric end stage renal disease patients
7. Long-term management of pre–end stage renal disease patients with severe cardiomyopathy who are in pulmonary edema or with acute kidney injury
8. Increasing anemia awareness and management

Figure 1
Heart-kidney interactions



who becomes volume depleted, whether it be from overly aggressive diuresis or an intercurrent volume-depleting illness. Third, ACE inhibitors or ARBs may induce acute kidney injury in patients with high-grade bilateral renal artery stenosis or stenosis of a dominant or a single kidney renal artery; in patients with extensive atherosclerotic disease in smaller preglomerular vessels; or in patients with significant luminal narrowing of afferent arterioles, as occurs with poorly treated hypertension or chronic calcineurin inhibitor use. More often than not, the complex nature of renal function changes in the CRS patient requires that ACE inhibitor or ARB therapy be temporarily stopped.

Many CRS patients are on the cusp of needing dialysis as their disease moves forward in what is sometimes an almost inexorable fashion; therefore, it must be determined whether a patient's clinical status has deteriorated enough that dialysis will be soon needed and, if so, which form of central access should be used for temporary dialysis. Once dialysis starts and a patient is brought to a euvolemic state and electrolyte abnormalities are corrected, a determination can be made as to whether dialytic intervention was merely a bridge therapy until improvement or whether long-term dialysis plans need to be initiated. The prevailing blood pressure often dictates the form of long-term dialysis that is considered. Maintenance hemodialysis can prove challenging in CRS patients with significant hypotension, and in such patients peritoneal dialysis may be the better dialytic modality (8). Of note, once end stage renal failure is determined to be present, it is not uncommon to have a role reversal in which the nephrologist becomes the primary health care provider and the cardiologist offers learned consultation.

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Cardiorenal Syndrome: The Cardiologist's Viewpoint

By Inder S. Anand, MD

Most cardiologists consider the coexistence of heart failure and chronic kidney disease (CKD) (1) or worsening of renal function (WRF) defined as an increase in serum creatinine >0.3 mg/dL (2) during treatment of acute decompensated heart failure (ADHF) as a reasonable working definition of cardiorenal syndrome (CRS). Others consider the presence of diuretic refractoriness despite persistent hypervolemia, inability to handle sodium load, and inability to use adequate doses of heart failure medications as important components of CRS. However, these variables have never been included in the definition because they are difficult to study. This brief review limits discussion to patients with type 1 (acute) and type 2 (chronic) CRS as proposed in a recent classification of CRS (3).

Prevalence and prognosis of cardiorenal syndrome

The prevalence of CKD (type 2 CRS) has been reported in the range of 32–50 percent in the large chronic heart failure trials (4–9). Population-based surveys in North America have found a similar prevalence of 38–56 percent (10–12). Gottlieb et al. found that the sensitivity and specificity for the prediction of poor outcomes with WRF, defined as a rise in serum creatinine of 0.3 mg/dL during ADHF (type 1 CRS), were 81 percent and 62 percent, respectively (2). Using that definition, the prevalence of type 1 CRS is reported in the range of 27–45 percent in previous studies (13–15). However, in the ADHERE registry, the prevalence of CKD (GFR < 60 mL/min/1.73 m^2) was as high as 65 percent (16).

The presence of CKD or the development of WRF are significant independent predictors of mortality and morbidity in patients with ADHF and chronic heart failure (4–12, 16–17). In the ADHERE registry, the in-hospital mortality increased from 1.9 percent for patients with normal renal function to 7.6 percent for patients with severe renal dysfunction ($p < 0.0001$) (16).

Predictors of cardiorenal syndrome

Several factors are associated with the presence of CRS in patients with chronic heart failure. In the Val-HeFT trial, the independent predictors for the presence of CRS were age, male gender, diabetes, ischemic etiology of heart failure, low blood pressures, worse neurohormonal and proinflammatory profile, presence of edema, and use of higher doses of diuretics (9).

Left ventricular ejection fraction did not predict the presence of CRS. Indeed, the presence of CRS was similar in patients with preserved (34 percent) or depressed (33 percent) left ventricular function in the CHARM trial, which studied the effects of the angiotensin receptor blocker candesartan in patients with depressed and preserved ejection fraction (6). The pathogenetic mechanisms responsible for the development of WRF during ADHF are not clear. Published studies have reported that baseline serum creatinine, coronary artery disease, hypertension, history of diabetes mellitus, use of calcium channel blockers, pulmonary edema, and high doses of diuretics are associated with its development (14,18–20). However, it is unclear whether the development of WRF is related to a pre-renal, intravascular volume depleted state, induced by intensive diuresis during the management of ADHF, or the result of a complex interaction involving heart failure treatment in the setting of intrinsic kidney disease. Other factors considered important in the pathogenesis of CRS are poor renal perfusion owing to low cardiac output, high venous pressure, and systemic and renal vasoconstriction (21,22).

Classical studies have taught us that low cardiac output activates catecholamine and the renin-angiotensin system, causing an increase in systemic and renovascular resistance, leading to a decrease in renal blood flow and GFR and to retention of salt and water (21). However, several hemodynamic studies in patients with ADHF have found that cardiac output is not necessarily low in these patients, although none of these studies directly assessed renal hemodynam-

> In low cardiac output states, auto-regulatory mechanisms help to maintain coronary and cerebral perfusion at the expense of other major organs including the kidneys, liver, and skeletal muscles.

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ics. In a study of 48 patients with ADHF, Weinfeld et al. did not find low cardiac output or estimated renal perfusion pressure (mean arterial minus CVP) in patients who developed CRS during heart failure treatment (23). In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization (ESCAPE) trial, cardiac output, pulmonary capillary wedge pressure, and systolic blood pressure did not correlate with renal function. Only right atrial pressure correlated weakly with baseline serum creatinine ($r = 0.165$, $p = 0.03$) (17).

Role of increased venous pressure in cardiorenal syndrome

Over 60 years ago Bradley and Bradley (24) showed that an increase in intra-abdominal pressure (IAP) to ~80 mm Hg obtained by applying a tight abdominal binder in normal volunteers caused an immediate decrease in effective renal plasma flow (ERPF), GFR, and urine output. Removal of the abdominal binders rapidly normalized the ERPF, GFR, and urine output. It is unclear whether raising the abdominal pressure caused an increase in renal venous pressure. However, in a series of elegant studies on isolated perfused kidney, Firth et al. (22) provided evidence that when arterial pressure is kept constant, an increase in renal venous pressure leads to a decrease in GFR.

In patients with ADHF, there is a potential for ascites and visceral edema that might increase the IAP. Intra-abdominal hypertension (IAH) (IAP >8 mm Hg) is associated with intra-abdominal organ dysfunction. The role of IAP in the pathogenesis of ADHF was recently investigated by Mullens et al. (25) in 40 patients with ADHF (LVEF 19 ± 9 percent, serum creatinine 2.0 ± 0.9 mg/dL), 60 percent of whom had elevated IAH. Elevated IAP was associated with worse renal function ($p = 0.009$). Intensive medical therapy resulted in improvement in both hemodynamic measurements and IAP. A strong correlation ($r = 0.77$, $p < 0.001$) was observed between reduction in IAP and improvement in renal function. However, changes in IAP or renal function did not correlate with changes in any hemodynamic variables (Figure 1). It appears, therefore, that elevated IAP is prevalent in a large number of patients with ADHF and is associated with impaired renal function. However, it is unclear whether high IAP is related to raised venous pressure.

To determine whether increased venous pressure rather than impairment of cardiac output is primarily associated with the development of WRF in patients with ADHF, the same inveatigators (26) studied 145 consecutive patients admitted with ADHF (age 57 ± 14 years, cardiac index 1.9 ± 0.6 L/min/m^2, LVEF 20 ± 8 percent, serum creatinine 1.7 ± 0.9 mg/dL). WRF developed in 40 percent of these patients. Patients who developed WRF had a higher central venous pressure (CVP) on admission (18 ± 7 mm Hg versus 12 ± 6 mm Hg, $p < 0.001$) after intensive medical therapy (11 ± 8 mm Hg versus 8 ± 5 mm Hg, $p = 0.04$). High venous pressure was the most important hemodynamic factor driving WRF in ADHF.

Is cardiorenal syndrome reversible?

In low cardiac output states, auto-regulatory mechanisms help to maintain coronary and cerebral perfusion at the expense of other major organs including the kidneys, liver, and skeletal muscles. The resulting poor renal perfusion contributes to renal dysfunction and has been considered important in the pathogenesis of CRS (21,22). However, studies in patients with chronic heart failure or ADHF have failed to show significant correlation between hemodynamic alterations and renal dysfunction apart from high venous pressure. These findings raise the question of whether intrinsic kidney disease plays a more important role in the pathogenesis of CRS and whether CRS reverses when hemodynamics improve.

Butler and colleagues (27) assessed the relationship between renal function in 220 patients who underwent left ventricular assist device placement. Creatinine clearance (CrCl) increased significantly within a week of left ventricular assist device placement suggesting that renal dysfunction is reversible even in patients with severe end stage heart failure (Figure 2).

Further support for the reversible nature of CRS comes from studies in patients with chronic constrictive pericarditis. The body fluid compartments, neurohormones, renal function, and hemodynamics were measured in 15 patients with CRS and constrictive pericarditis before and eight weeks after pericardiectomy. Pericardiectomy rapidly normalized the hemodynamics, neurohormones, body fluid compartments, and renal dysfunction. The cardiac index increased from 2.0 ± 0.2 to 3.6 ± 0.3 L/min/m^2, right atrial pressure fell from 22.1 ± 1.2 mm Hg to 5.3 ± 0.7 mm Hg, ERPF increased from 243 ± 21 to 382 ± 34 L/min/1.73 m^2, and serum creatinine fell from 1.5 to 1.0 mg/dL (28). Taken together these data underscore the importance of hemodynamics in the pathogenesis of CRS and demonstrate that in many patients renal dysfunction is reversible if the hemodynamics can be improved.

Conclusions

CRS is very common in patients with ADHF or chronic heart failure and is an independent predictor of poor clinical outcomes. The exact prevalence of structural kidney disease in CRS is unknown but is likely to be high because of the common association of atherosclerotic CV disease, diabetes, and hypertension with heart failure. Although low cardiac output-induced neurohormonal activation in heart failure reduces renal blood flow and is probably an important factor contributing to renal dysfunction, the exact role of hemodynamic mechanisms is not entirely clear.

Increasing data suggest that elevated venous pressure may contribute to renal dysfunction in heart failure. In many patients, renal dysfunction does normalize when the pump function improves. In others, the underlying structural renal disease may contribute to permanent renal dysfunction. Further studies are required to improve our understanding of the complex interactions between heart failure and renal dysfunction to enable us to devise better therapies for CRS.

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Figure 1

Intra-abdominal pressure (IAP) is increased in a significant number of patients with ADHF. The left half of the graph shows that elevated IAP is associated with worse renal function. Note a strong correlation between reduction in IAP and improved renal function in patients with baseline elevated IAP (Redrawn from Mullens et al. *J Am Coll Cardiol* 2008; 51:300–6).

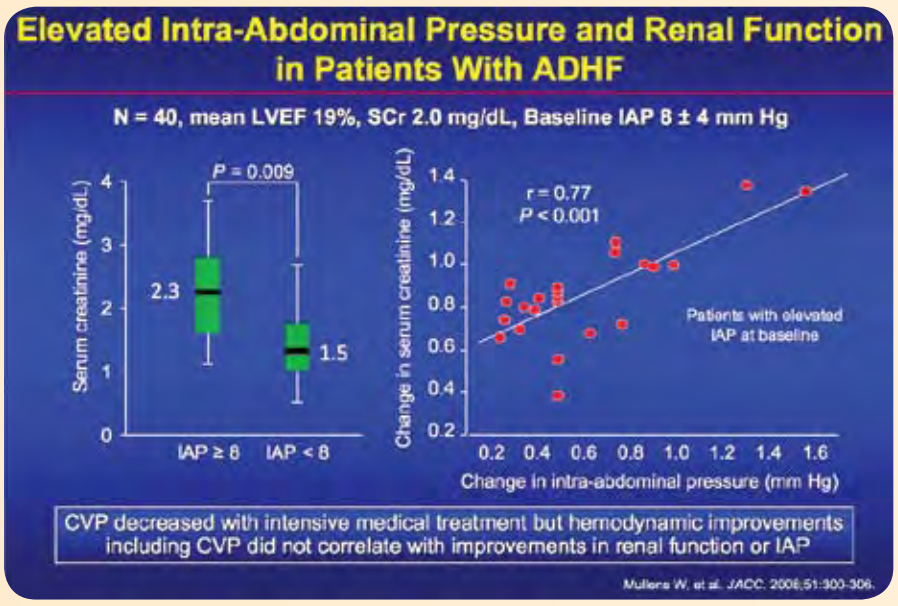
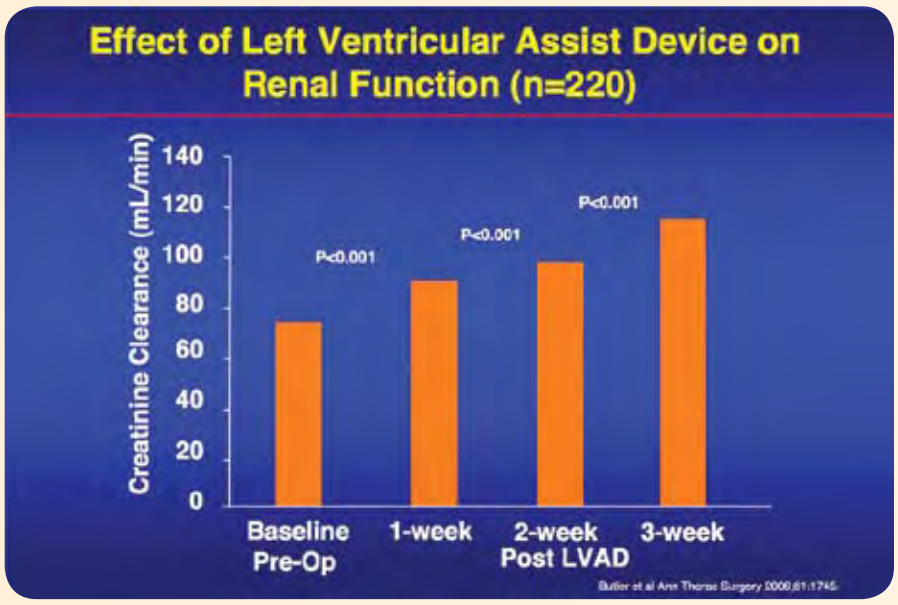


Figure 2

Renal function (creatinine clearance) improved substantially and rapidly in post-LVAD survivors (from Butler J, et al. *Ann Thorac Surg*; 81:1745–1751).



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Anemia Management in Cardiorenal Disease

By Donald S. Silverberg MD, Dov Wexler MD, Adrian Iaina, MD, and Doron Schwartz, MD

Anemia is common in congestive heart failure (CHF) and is associated with increased mortality, morbidity, and progressive renal failure. The two most common causes of the anemia are associated renal failure, which causes depression of erythropoietin production in the kidney, and excessive cytokine production, which can also cause depression of erythropoietin production in the kidney as well as depression of the erythropoietic response in bone marrow.

Cytokines can induce iron deficiency by increasing hepcidin production from the liver, which both reduces gastrointestinal iron absorption and reduces iron release from iron stores located in the macrophages and hepatocytes. Many studies of anemia in CHF with erythropoiesis stimulating agents (ESA) and oral or IV iron—but also with IV iron without ESA—have shown positive effects on the anemia as well as on hospitalization, fatigue and shortness of breath, cardiac and renal function, quality of life, exercise capacity, and reduced beta natriuretic peptide. These studies have not demonstrated an increase in cardiovascular damage related to the therapy. Adequately powered, long-term placebo-controlled studies of ESA and of IV iron in CHF are still needed to examine hard cardiovascular endpoints.

Prevalence and significance of anemia in CHF

In a recent meta-analysis of 34 studies of anemia in CHF (1) including a total of 153,180 patients, 37.2 percent were anemic (using the authors' own criteria), and the adjusted hazard ratio (HR) for death was 1.46. In these anemic CHF patients, there was no difference between systolic or diastolic CHF in prevalence of anemia or mortality.

Another recent meta-analysis looked at 21 prospective clinical studies of anemia in CHF that studied 97,699 patients (2) (Table 1).

In the six studies that considered mortality, anemia was linked to a significantly higher risk of death (rr 1.66, $p < 0.001$). In three of the four studies that looked at CHF hospitalization rates, the rates were higher among anemic patients. In the five studies that evaluated left ventricular ejection fraction (LVEF), anemic patients had a 0.53 percent lower LVEF than nonanemic patients, $p < 0.001$. In 16 of the 21 studies that used multivariate analysis, an independent relationship between anemia and all outcomes in CHF was found.

These studies suggest but do not prove that anemia plays a causal role in the worsening of CHF.

What causes the anemia in CHF?

Anemia associated with CHF is most likely due to a combination of several factors (3,4).

Chronic kidney disease (CKD)

CKD is associated with reduced production of erythropoietin (EPO) in the kidney. The renal damage seen in many cases of CHF is probably mainly a result of reduced renal blood flow caused by the reduced cardiac output leading to hypoxic renal damage. Perhaps the most dramatic evidence of the role of CHF in renal failure is the improvement of renal function seen after successful cardiac resynchronization therapy when cardiac function is improved. Treatment of CHF with beta blockers is associated with an improvement in CHF and with an improvement in renal function and anemia (5). These data suggest that the better CHF is treated, the slower will be the progression of renal failure.

Elevated cytokines causing abnormalities in EPO and iron metabolism

Cytokines elaborated in CHF, especially tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6), can cause four hematological abnormalities (6):

- reduced EPO production in the kidney leading to inappropriately low levels in the blood for the degree of anemia present
- reduced erythropoietic response of the bone marrow to ESA

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- hepcidin-induced failure of iron absorption from the gut
- hepcidin-induced trapping of iron in iron stores in the macrophages and hepatocytes

Hepcidin (6) is a protein released from the liver by IL-6. It inhibits the protein ferroportin, which is found in the gastrointestinal tract and in macrophages and hepatocytes. Ferroportin is responsible for the release of iron from these three types of cells into the blood. If ferroportin is inhibited, gastrointestinal iron absorption is diminished, and iron is not released from its storage in macrophages and hepatocytes. This results in a low serum iron, leading to decreased delivery of iron to bone marrow and therefore iron deficiency anemia, even in the presence of adequate total iron stores—the so-called functional iron deficiency. Since hepcidin is filtered and removed in the kidney, its levels increase in CKD, which also partly explains the iron deficiency in CKD and CHF.

Compared to hemodialysis patients taking EPO alone, those taking EPO and IV iron had lower proinflammatory TNFα levels and higher anti-inflammatory cytokine IL-4 levels as well as lower levels of total peroxide (a marker of free radical concentration) (7) suggesting that iron may be anti-inflammatory.

Use of angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), and beta blockers

ACE-I and ARBs can each cause a fall in hemoglobin (Hb) of about 0.5–1g/dL due to reduced production of EPO and reduced activity of EPO in the bone marrow, because angiotensin is a stimulator of erythropoiesis (8). ACE-I can also increase the levels of erythropoietic inhibitors in the blood, further inhibiting erythropoiesis. ACE-Is and ARBs are additive and equal in their effect on reducing the Hb. They are often used together, and can therefore cause a fall in Hb of about 1–2 g/dL (8).

Hemodilution

It has been suggested that the anemia in CHF in many cases is partly due to hemodilution. In one study (9), investigators found that a true red cell deficit was present in 88 percent of CHF patients with anemia and diastolic CHF and 59 percent of those with anemia and systolic CHF. All the systolic CHF patients and 71 percent of the diastolic CHF patients also had expanded plasma volume. All these studies suggest that there is a true red cell deficit in the majority of anemic CHF patients but that hemodilution is also very common.

Diabetes

The EPO-producing cells in the kidney may be damaged early by glycosylation, which can explain why, for the same degree of renal function, diabetics have a lower Hb than nondiabetics.

Gastrointestinal problems

These include bleeding from aspirin, clopidogrel, warfarin-like agents, malignant tumors, polyps, esophagitis, or reduced iron absorption resulting from atrophic gastritis (in some cases caused by *Helicobacter pylori*, which can also cause Vitamin B12 deficiency), or from CHF-induced edema and damage to the intestinal wall. It has also been found that proton pump inhibitors such as omeprazole, which are widely used, reduce iron absorption.

Effect of correcting anemia in CHF patients with ESA

The studies of patients with CHF in whom the anemia has been treated have used either ESAs such as EPO or its derivative, the longer acting DA, along with the addition of either oral or intravenous (IV) iron. Such treatment has been reported in uncontrolled studies, non-placebo-controlled studies, small single-blind and small double-blind, placebo-controlled studies, or larger double-blind placebo-controlled studies (10). A recent Cochrane review (10) of ESA in CHF identified 11 RCTs with 793 participants comparing ESA with control. Nine of the studies were placebo-controlled, but only five were double blind. ESA treatment compared to control treatment was associated with an increase in Hb of about 2 g/dL, and the treatment was significantly associated with

- fewer heart failure-related hospitalizations: rr 0.70 (0.5–0.93)
- lower all-cause mortality: rr 0.59 (0.36–0.96)
- improved exercise duration: 96.8 s
- improved walk distance: 69.3 meters
- increased peak exercise oxygen consumption: 2.29 mL/kg/min
- improved NYHA class by a mean of 0.73
- improved ejection fraction: +5.8 percent
- reduced BNP: 236.6 pg/mL
- improved quality of life indicators

However, no meta analysis can take the place of adequately powered long-term placebo-controlled studies with solid and not just surrogate endpoints, and no such study has as yet been completed for ESA in CHF.

Table 1. Findings from a meta-analysis of 21 studies of anemia in CHF

1. the prevalence of anemia using the WHO criteria varied from 10 to 58 percent
2. the anemic patients were 3.08 years older than the nonanemics, p <0.001
3. the anemic patients compared to nonanemics had:
   - a higher frequency of ischemic heart disease: RR 1.17, p<0.01
   - more diabetes: RR 1.27, p<0.001
   - a higher serum creatinine: 20.46 μmol/L, p<0.001
   - a lower glomerular filtration rate of 8.15 mL/min/1.73 m^2, p<0.001
   - a lower serum sodium: 1.01 mEq/L, p<0.001
   - a lower BMI
   - a 35 percent greater chance of having more severe CHF-NYHA class (III or IV), p<0.001

Other effects of ESAs in CHF

Several studies have shown that correction of the anemia with ESA improved renal function, reduced diuretic dose, reduced heart rate, improved caloric intake, improved depression, and improved sleep apnea. Correction of the anemia also reduced plasma volume, increased red cell volume, improved left ventricular systolic and diastolic function, reduced left ventricular hypertrophy and dilation, reduced pulmonary artery pressure and severity of mitral regurgitation, reduced oxidative and nitrosative stress, reduced inflammatory factors such as IL-6 and C-reactive Protein (CRP), and improved adhesive and proliferative properties of circulating endothelial progenitor cells (3,4).

Adverse effects

A pooled analysis of three placebo-controlled DA studies (11–15) (which had a target Hb of 14±1 g/dL) consisting of 516 patients found no differences in the rate of adverse effects or death compared to placebo. No significant differences occurred in mortality or in the incidence of hypertension, venous thrombosis, pulmonary embolus, cerebrovascular disorder, myocardial infarction, or other cardiovascular events. This held true even in those with more severe renal failure or more severe heart failure (15). Similarly, in the Cochrane meta-analysis of ESA in CHF mentioned above (10), no increase in adverse effects was observed. However, the studies examined were small and of limited duration.

The nonhematopoetic biological effects of erythropoietin

The value of ESAs in CHF has been shown in animal studies where its use after a myocardial infarction or after production of cardiac damage by other means—with or without improving the Hb—has improved endothelial dysfunction, increased neovascularization of heart muscle, reduced apoptosis of cardiomyocytes, reduced oxidative stress and inflammation, reduced fibrosis, reduced hypoxic damage, and prevented functional impairment of the heart (16). At least some of these effects are due to the increase in number and activity of endothelial progenitor cells from the bone marrow.

The effect of IV iron alone in the anemia of CHF

Experimental studies in animals have shown that severe iron deficiency can cause diastolic dysfunction and heart failure with pulmonary congestion, left ventricular hypertrophy and dilation, cardiac fibrosis, a reduction in EPO levels, and a worsening of the molecular signaling pathways (as measured by cardiac STAT 3 phosphorylation), an increase in the inflammatory cytokine TNFα, and proteinuria (17). In addition, iron deficiency in rat hearts causes mitochondrial ultrastructural aberrations, irregular sarcomere organization, and release of cytochrome C (18).

The prevalence of iron deficiency in CHF depends on how iron deficiency is defined. If merely defined as a percent transferrin saturation (percent TSAT) of <16 percent, it was found in one preliminary study in 78 percent of anemic and 61 percent of nonanemic CHF patients. If defined as a percent TSAT of <16 percent and a serum ferritin of 30–100 μg/L, it was found in only 15 percent of anemics and 15 percent of nonanemics (21).

In another study of anemia in CHF, about half the patients had serum iron below normal, and the great majority of anemic patients also had an elevated soluble transferrin receptor (a quite dependable measure of iron deficiency) (22). Markedly reduced iron stores were in the bone marrow in 73 percent of the cases in a study of anemia in severe CHF (23). Therefore pure iron deficiency (serum ferritin <100 μg/L and transferrin saturation <20 percent) or functional iron deficiency (serum ferritin >100 μg/L and percent TSAT <20 percent)

are commonly seen in CHF patients with anemia or even without anemia.

Does IV iron improve iron-deficient CHF patients?

Three recent studies of IV iron in anemic CHF patients—two uncontrolled studies (24,25) and one double-blind placebo-controlled study (26)—have found improved Hb, hospitalization, LVEF, NYHA class, quality of life, left ventricular hypertrophy and dilation, exercise capacity, and renal function, as well as reduced heart rate, BNP, and CRP.

In another recent CHF controlled study of IV iron in patients with iron deficiency with or without anemia, there was an improvement in NYHA class, Patient Global Assessment, and oxygen consumption during exercise (27), even though the Hb did not improve significantly with IV iron. These changes were more pronounced in the anemic patients, suggesting that part of the effect of iron on the heart may be related not only to its causing improved oxygenation from the increased Hb but also to iron's direct effects on improving mitochondrial function, resulting in increased oxygen utilization and increased ATP and energy production.

A multicenter double-blind, placebo-controlled study of 459 CHF patients with iron deficiency anemia using IV iron alone, the FAIR-HF study (28) has recently been published. In this study, an improvement was seen in the NYHA, patient global assessment, six-minute walk test, Quality of Life, and renal function with the use of IV iron alone. There was also a trend toward a lower rate of first hospitalization for any cardiovascular reason among those receiving the IV iron compared with those receiving placebo. These positive findings were similar in those with anemia and those without anemia.

In most studies comparing oral to IV iron in CKD, IV iron has been found to produce a greater Hb response with fewer side effects (29). No comparisons have been made between oral and IV therapy in CHF.

If iron is to be used in the anemia of CHF, in our opinion, it is probably best to use the IV form. But as in the case of ESA, there are no long-term placebo-controlled studies of IV iron with solid endpoints. Until these studies are done, there will be uncertainty about the value of iron therapy in CHF.

To what level should Hb be corrected in CHF?

U.S. FDA guidelines for ESA products are not available for CHF but are available for CKD. In light of safety concerns about raising Hb levels above 12 g/dL with ESA, the guidelines state that dosing should be individualized to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL and that higher doses of these agents should be avoided. It is hoped that the role of target Hb levels above 12 g/dL in CHF treated with ESA will be clarified by the long-term placebo-controlled study with more than 2000 patients, The Reduction of Events with Darbepoetin alfa in Heart Failure, the RED-HF study (30), due for completion in 2011.

Conclusions

Faced with patients who have both CHF and Hb levels below 12 g/dL, it may well be that ESA use should be considered to raise the Hb to 12 g/dL. If iron deficiency is present, as it often is, correction with IV iron even without ESA may also be a useful intervention and might even be used as the first therapy applied. Correction of iron deficiency even without the presence of anemia may also be indicated, but here again data is lacking.

It may well turn out that a combined approach of ESA and IV iron is the best approach for correcting the anemia in CHF. This will allow a lower dose of both agents to be used, which will reduce the chances of side effects caused by high doses of either agent, reduce the dose and cost of ESA, cause a more rapid and greater Hb response than that achieved with either agent alone, increase the chances of reaching the target hemoglobin, and reduce the chances of iron deficiency being induced by ESA. Clearly, the relative role of ESA and/or IV iron in the treatment of the anemia of CHF merits further investigation by long-term placebo-controlled studies with hard endpoints. Finally, it should be said that good treatment of CHF is associated with an improvement in renal function or a slowing in its progression. Therefore, cooperation between the nephrologist and cardiologist in the treatment of patients with CHF is crucial.

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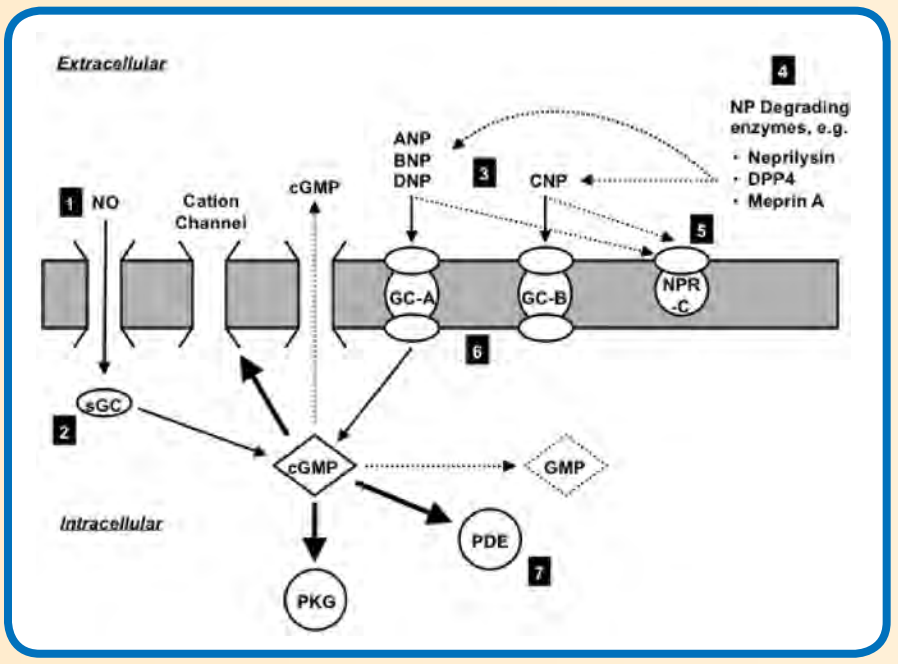
Novel Natriuretic Peptides and the Cardiorenal Syndrome

By Fernando L. Martin, MD, and John C. Burnett, Jr., MD

Renal dysfunction in heart failure patients or the presence of cardiac functional impairment in renal failure patients invariably means a worsening prognosis in either setting (1–7). Clinical and experimental studies have concluded that there is not one unique mechanism for cardiorenal syndrome. Decreased renal perfusion in the heart failure setting has been a ssociated with renal hypoxia, increased sympathetic activity, elevated central venous pressure and increased intra-abdominal pressure, oxidative stress, endothelial dysfunction, as well as with activated renin-angiotensin-aldosterone system (RAAS) and vasopressin system (REF) (8–13).

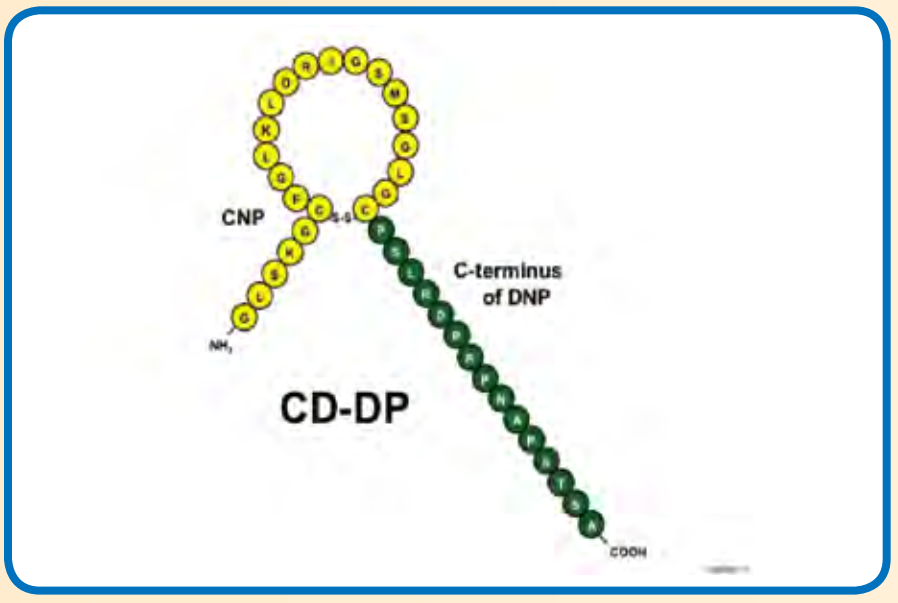
Beyond elucidating the mechanisms of this syndrome, there is an unmet need for innovative therapeutics that aim both at the heart and the kidney to enhance both organ systems in the control of optimal cardiorenal function. Indeed, the goal of a cardiorenal therapeutic should be to 1) unload the heart including decreasing venous pressure while minimizing reductions in blood pressure, 2) directly target the nephron to preserve or enhance glomerular filtration rate (GFR) and reduce salt and water retention, and 3) suppress activated RAAS and arginine vasopressin (AVP) systems.

Figure 1. Guanylyl cyclase (GC) pathways, activation of cGMP as their second messenger



Nitric oxide (NO) activates soluble GC. ANP, BNP, and DNP stimulate GC-A, while CNP stimulates GC-B. NPs also bind to the non-GC linked NP clearance receptor (NPR-C). Cyclic GMP modulates cGMP-dependent protein kinase G (PKG), cGMP-regulated phosphodiesterases (PDEs), and cGMP-regulated cation channels. The cGMP signal is terminated by PDEs that hydrolyze cGMP to GMP. The NPs are degraded by peptidases such as neprilysin (also known as neutral endopeptidase 24.11), dipeptidyl peptidase IV (DPP4), and meprin A. Strategies to enhance cyclic GMP signaling therapeutically include 1) the use of NO-mimetics such as nitro vasodilators, 2) direct sGC stimulators, 3) exogenous native and designer NPs, 4) inhibiting NP degrading enzymes, 5) blocking NPR-C, 6) overexpressing GC-A or GC-B or both; and 7) inhibiting the activity of cGMP-hydrolyzing PDEs.

Figure 2. CD-NP



The structure of CD-NP combines the mature 22-amino acid structure of CNP and the 13-amino acid C-terminus of DNP representing a dual activator of GC-A and GC-B with receptor affinities (GC-B<GC-A) (24).

Among this family of peptides, the only approved for therapeutic use in the United States is BNP (nesiritide), specifically in the setting of acute decompensated heart failure (ADHF). BNP is a GC-A receptor agonist with potent arterial vasodilating properties. It enhances renal function in conditions such as cardiopulmonary bypass surgery, but in ADHF and because of excessive hypotension it may impair renal function. It is hoped that the resulting controversy will be clarified soon by completion of the ASCEND-HF trial in patients with ADHF, which will address the safety and efficacy of nesiritide in 7000 individuals randomized to BNP or standard care (17) .

The aim of improving natriuretic peptide therapy in terms of safety and efficacy led to the design of a novel chimeric natriuretic peptide that unloads the heart but does not cause excessive hypotension while enhancing renal function. This peptide, CD-NP, is currently being tested in phase II trials. CD-NP is a designer NP that integrates mature CNP with the C-terminus of DNP (18–20). The rationale for the design of CD-NP is based on the vascular actions of CNP, produced by the endothelium and acting through GC-B, which possesses venodilatory properties causing less hypotension than ANP (19).

CNP also accelerates endothelial repair and is potently antifibrotic. It inhibits hypertrophy in cardiomyocytes but is not natriuretic nor does it suppress the RAAS (21). CNP lacks a C-terminus, making it very susceptible to degradation by neutral endopeptidase (NEP), the enzyme that degrades natriuretic peptides. DNP, on the other hand, is a natriuretic peptide that was originally found in a snake, the *Dendroaspis angusticeps* (Eastern Green Mamba) (22). This peptide binds to the GC-A receptor, the same receptor that ANP and BNP bind to, giving it natriuretic and diuretic properties. Importantly, the 15-amino acid C-terminus confers high resistance to degradation. CD-NP therefore is a designer chimeric natriuretic peptide, the first of its kind, that represents a dual GC-A and GC-B receptor agonist (18,19). Thus, CD-NP was engineered to exploit the characteristics of CNP so that CD-NP would be less hypotensive than BNP and possess renal-enhancing, cardiac preload-reducing, and RAAS-suppressing actions.

Preclinical studies in the laboratory showed that in plasma and urine, CD-NP compared to CNP had enhanced cGMP generation (18). In a different preclinical study, comparison to BNP showed that CD-NP had less hypotensive effects than BNP and that it possessed GFR-enhancing properties (18,19). Moreover, CD-NP reduced cardiac filling pressures and suppressed renin. In healthy insdividuals, CD-NP increased cGMP production in plasma as well as in urine compared to placebo. It also increased urinary sodium excretion without excessive hypotension, and it decreased aldosterone plasma levels. In preliminary studies in patients with heart failure, CD-NP improved GFR estimated from creatinine clearance, reduced cardiac filling pressures as demonstrated by a reduction in plasma, and suppressed aldosterone (19).

Recently, a second designer natriuretic peptide based on a genomic approach has been reported (23,24). In this case, based upon alternative splicing of the BNP gene, a BNP-like peptide was discovered and has been called AS-BNP. Owing to intron retention, alternative splicing codes for a unique 34-amino acid C-terminus while preserving the remainder of native BNP. From AS-BNP, a novel shorter amino acid peptide was designed that results in a renal-selective action. In experimental heart failure, this designer peptide (AS-BNP.1) enhances GFR, increases sodium excretion, and suppresses renin. Importantly, it has no effect on blood pressure, which is preserved (23). It is hypothesized that this second designer peptide may activate a novel renal natriuretic peptide receptor. Clinical trials are expected to start soon.

The cardiorenal syndrome will continue to be a clinical challenge. We still need to understand its mechanisms and seek more effective and safe therapies.

The native natriuretic peptides and their respective cGMP-linked receptors possess renal-enhancing actions but are limited by untoward effects on the kidney. Novel drug discovery and design taking key parts of native natriuretic peptides and creating designer drugs like CD-NP may optimize renal-favorable effects such as renal protection and limit adverse actions such as excessive hypotension but still unload the heart. Second, use of genomic research tools may provide opportunities to find novel natriuretic peptides resulting in the engineering of renal-specific peptides such as AS-BNP.1, which may prove efficacious in the cardiorenal syndrome. We all await exciting results of new and ongoing trials of these novel natriuretic peptides for cardiorenal disease.

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Treatment Options in Cardiorenal Syndrome

By Adel Berbari, MD

Interaction between chronic kidney disease (CKD) and cardiovascular disease (CVD), termed the cardiorenal syndrome (CRS), is characterized by enhanced risk of atherosclerosis and uremia-related myocardial disorders (Figure 1). While milder degrees of renal impairment (CKD stages 1–3) are associated with accelerated risk of atherosclerotic events, a uremia-specific cardiomyopathy characterizes the more severe and advanced stages of renal dysfunction and end stage renal disease (ESRD) (stages 4, 5, and ESRD) (Figure 1).

Therapeutic options in CRS depend on the severity of the degree of renal impairment and associated clinical conditions.

In CKD stages 1–3, the goal of therapeutic approaches is directed at controlling atherosclerotic comorbidities, while in CKD 4, 5, and ESRD, the aim of therapy is to improve the general condition of the patient.

Atherosclerosis

To reduce the impact of the cardiorenal syndrome on CVD morbidity and mortality, the following therapeutic strategies are currently recommended:

- blood pressure (BP) control
- albuminuria reduction
- dyslipidemia and statin therapy
- antiplatelet agents
- vitamin D–calcium–phosphorus control

Blood pressure control

Long-term cardiorenal protection involves two important concepts: BP control to a much lower target of systolic BP < 130 mmHg and use of an agent that blocks the renin-angiotensin-aldosterone (RAAS) system as base therapy. However, appropriate BP control becomes more difficult as kidney function declines. In addition, patient with CKD also have increased rates of uncontrolled hypertension.

Antihypertensive therapy should be initiated with an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). The antihypertensive regimen can be further modified according to BP-lowering efficacy and CVD reduction. Coadministration of diuretics is mandatory: thiazides in early/mild stages and loop diuretics when serum creatinine > 2.5 mg/dL. Potassium-sparing diuretics are contraindicated. Addition of beta blockers affords cardioprotective benefits such as angina reduction, improved left ventricular function, reduced rates of hospitalization and reduced rates of sudden death in patients after myocardial infarction and in those with concurrent heart failure.

The current consensus is to lower SBP to at least 130 mm Hg. However, further reduction may be unsafe, particularly in high risk patients as it has been associated with increased CVD risk.

Albuminuria

Reduction of albuminuria, a treatment target associated with improved cardiovascular and renal outcomes, can be achieved by BP reduction with RAAS blockade.

However, in a substantial number of patients, albuminuria > 1 g/day persists despite SBP < 130 mmHg and continued RAAS blockade. This condition results from secondary increase in aldosterone production and responds to addition of spironolactone or eplerenone on top of RAAS blockade.

Dyslipidemia and statin therapy

Patients with CKD and ESRD exhibit a pattern of mixed dyslipidemia characterized by decreased high density lipoprotein cholesterol (HDL-C), increased triglycerides, and increased low-density lipoprotein cholesterol (LDL-C). The National Kidney Foundation's (NKF) recommended target goals for treating dyslipidemia in patients with CKD are: total cholesterol < 200 mg/dL, LDL-C <100 mg/dL, HDL-C > 40 mg/dL.

NKF recommends lifestyle changes in accordance with pharmacotherapy. Based on the lipid pattern of dyslipidemia most commonly found in CKD, with elevated triglycerides and low HDL-C, treatment with nicotinic acid and fibrate is indicated. However, fibrate use in patients with ESRD has been linked to rhabdomyolysis, possibly generating additional acute renal failure.

For reduction in LDL-C, statins are first-line agents. These drugs are well tolerated and safe. They have been shown to reduce cardiovascular events and mortality in CKD patients, and to attenuate declines in renal function and increase in albuminuria. Although considered safe for use in CKD, dose reduction is re-

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quired with the use of lovastatin, rosuvastatin, and simvastatin. The metabolism of statins is altered by certain filtrates, increasing the risk of myopathy when drugs from these two classes are used concurrently.

Antiplatelet agents

The use of aspirin at 81 mg/day in renal patients is safe and is associated with cardiovascular protection. In patients intolerant to aspirin, clopidogrel is generally recommended. Although it inhibits platelet aggregation, clopidogrel lacks the benefit of cardiovascular protection in CKD patients.

Vitamin D—calcium—phosphorus metabolism

Normalizing the concentration of the precursor molecule 25(OH)D3 if less than 30 mg/mL with active vitamin D drugs (Cholecalciferol) is recommended, as is normalizing serum phosphate by oral phosphate binders or intestinal phosphate transport.

Cardiomyopathy

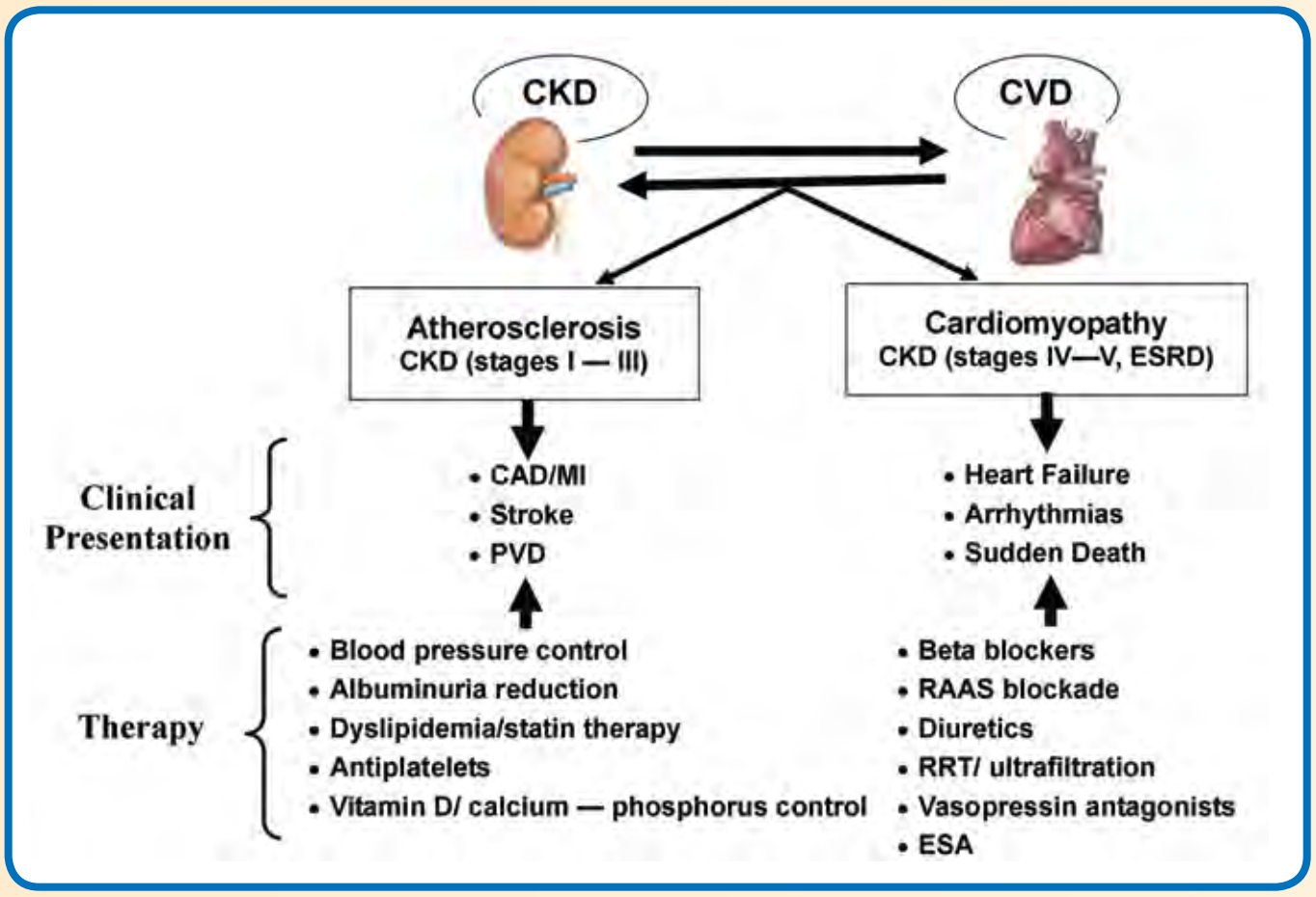
Chronic heart failure (CHF) occurs in about 25 percent of patients with ESRD and accounts for 50 percent of cardiovascular disease (CVD) mortality. In ESRD, CHF results from a uremia-specific type of cardiomyopathy. Its prevalence increases with further deterioration of renal function and may progress to an ominous state of acute decompensated heart failure (ADHF).

The heterogeneous and complex pathophysiology of cardiorenal dysfunction in these patients makes management an intricate clinical challenge. To date, there is no single therapeutic approach guaranteed to succeed, because of the unique risk profile and combination of co-morbidities in each patient.

General measures

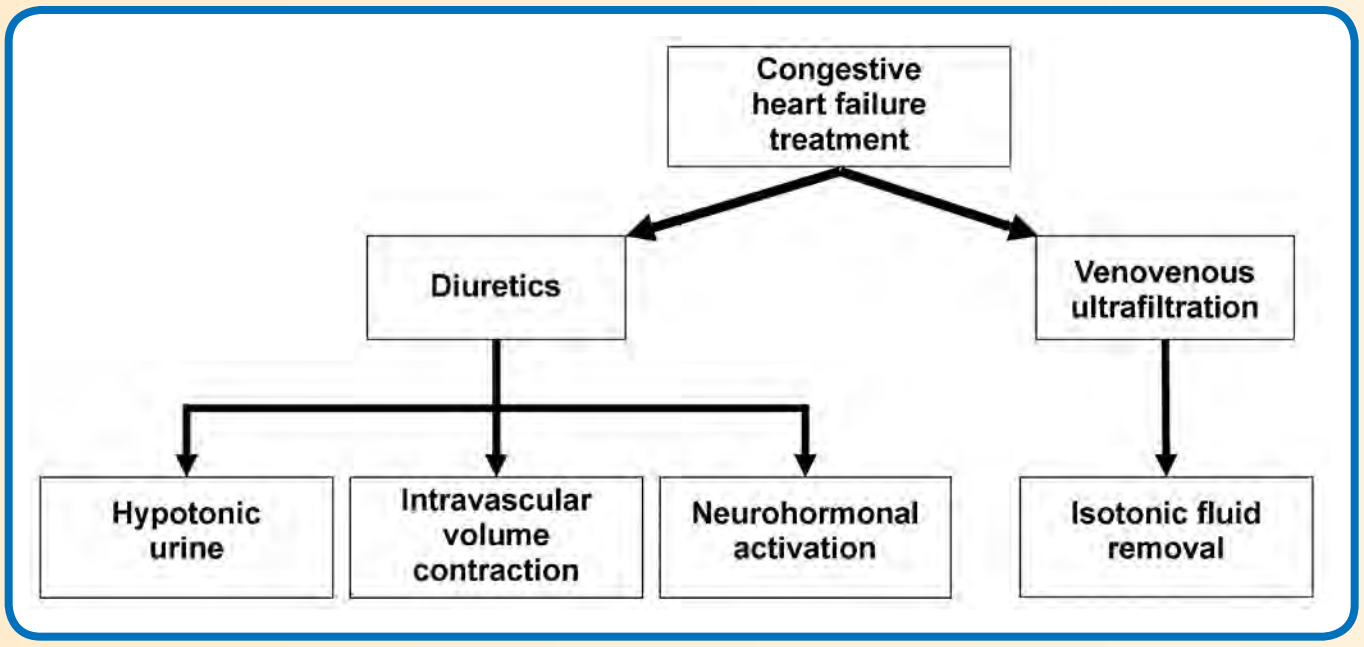
The patient needs continuous hemodynamic monitoring, especially if BP is low and the filling pressure uncertain. Body weight, the single most important indicator, should be recorded frequently.

Figure 1. Cardiorenal syndrome: clinical presentation and therapeutic options



Abbreviations: RRT, renal replacement therapy; PVD, peripheral vascular disease; ESA, erythropoiesis-stimulating agents

Figure 2. Modalities of therapy in congestive heart failure in chronic kidney disease



It is advisable to restrict intake of free water to less than 1000 mL per 24 h if the patient is hyponatremic. In some patients with low BP and low filling pressure, volume expansion may be required.

Diuretic therapy and resistance

Diuretics remain the mainstay of the management of fluid overloaded patients with heart failure and ADHF.

Loop, thiazide and potassium-sparing diuretics provide diuresis and natriuresis within 20–30 minutes of administration. When administered orally or parenterally these drugs must be secreted actively, and not passively filtered into the renal tubules to exert their desired effects of blocking sodium reabsorption in the renal tubules. In patients with renal insufficiency, higher doses of loop diuretics are needed to achieve the same level of natriuresis. In contrast, the use of thiazide diuretics as monotherapy is markedly reduced in states of renal dysfunction with GFR under 30 mL/min/1.73m^2.

Diuretics provide effective short-term symptomatic relief. However diuretic use exacerbates neurohormonal activity, which often leads to postdiuresis sodium retention and further renal dysfunction, limiting their effectiveness (diuretic resistance). In ADHF, this resistance can be managed by continuous intravenous infusions, rather than bolus doses, of furosemide starting at 5 mg/h to 10 mg/h following an intravenous thiazide diuretic (often primed with 250–500 mg intravenous chlorothiazide). To avoid the risk of ototoxicity, the high doses of furosemide should be administered slowly over 30 to 60 min.

If the patient is resistant to furosemide, the efficacy can be improved by the addition of salt-poor albumin to the infusion. The resulting furosemide-albumin complex is believed to deliver more diuretic to the kidney, primarily by remaining in the vascular space. Adding salt-poor albumin has been shown to substantially increase sodium excretion.

Vasodilator therapy

Intravenous nitroglycerin or nesiritide have been used to alleviate pulmonary congestion in patients with ADHF. These drugs are effective in reducing myocardial oxygen demand by reducing central venous and ventricular filling pressures, and improving cardiac output by reducing systemic vascular resistance.

Of particular importance is nesiritide, a vasodilator with mild diuretic effects. There has been much debate on benefits and risks of nesiritide. Recent studies, however, indicate that at low doses, nesiritide causes no risk to kidney function and in some cases, it may be renoprotective. When used in doses of 0.005–0.01 µg/kg/mL, nesiritide poses no additional risks to renal function and, even may afford cardiorenal protection when administered in doses of 0.0025–0.005 µg/kg/mL without an initial bolus.

Renal replacement therapy (RRT)/ ultrafiltration

Given the multiple difficulties and frequent failure with diuretics in the management of heart failure, alternative strategies for

the treatment of fluid overload have been explored, including the use of mechanical means. The most notable development in this respect has been veno-venous ultrafiltration. In contrast to diuretics that produce hypotonic urine and intravascular volume contraction, leading to further sodium and water retention, ultrafiltration results in the removal of isotonic fluid without causing neurohormonal activation or disturbances in serum electrolytes (Figure 2). In the Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) study, ultrafiltration achieved greater fluid and weight loss than intravenous diuretics, reduced 90-day rehospitalization and unscheduled visits, and appeared to be an effective alternative therapy. The effect of ultrafiltration on mortality, however, remains to be established.

Renin Angiotensin Aldosterone (RAAS) blockade

Owing to extensive and multiple detrimental effects of chronic RAAS activation, RAAS inhibition has emerged as a mainstay of treatment for patients with heart failure. Angiotensin converting enzyme (ACE) inhibitors improve symptoms of heart failure and reduce morbidity and mortality. Despite a mild reduction in GFR due to blunting of angiotensin II-induced vasoconstriction of the efferent arterioles, ACE inhibitors preserve renal function long-term. However ACE inhibitors should be used cautiously, starting with small doses, in patients with renal insufficiency in order to prevent marked deterioration in renal function.

An alternative mechanism of blocking the effects of angiotensin II is with ARBs, either in place of or in addition to ACE inhibitors. Both of these strategies have been reported to benefit patients with heart failure.

Although both ACE inhibitors and ARBs reduce aldosterone production, further aldosterone inhibition with specific aldosterone antagonists provides additional benefits. They block renal sodium and water reabsorption, reduce fibrosis in the kidney and in the heart helping to preserve cardiorenal function, and reduce significantly mortality in advanced heart failure. However, they should be used cautiously in patients with significant renal dysfunction to prevent hyperkalemia.

Aliskiren, a direct renin inhibitor, has been shown to reduce BNP levels. Urinary aldosterone in heart failure patients already on ARB and ACE inhibitors (Aliskiren Observation of Heart Failure Treatment [ALOFT]) may be considered a therapeutic option in such patients.

Inotropes

A trial of inotropic therapy using dopamine or milrinone may be considered in renal impaired patients with low cardiac output. However, the use of inotropes in these patients has not been associated with improved survival.

Vasopressin (antidiuretic hormone [ADH]) antagonists

In heart failure, low BP and contracted effective arterial blood volume enhance vasopressin (ADH) secretion which, by acting on selective renal V2 receptors, promotes increased water reabsorption and hyponatremia.

Studies have shown that vasopressin antagonists, known as vaptans (such as Tolvaptan), are beneficial in the short term by inducing greater reduction in body weight, increased urine output and increased serum sodium, but with no proven efficacy in the long term. Thus, the use of vasopressin antagonists may be recommended in the acute setting, but will probably not influence disease attenuation and recovery.

Beta blockers

Prescription of beta blockers is recommended to patients with CKD and heart failure. These drugs retard the progression of left ventricular disease and reduce recurrent myocardial infarction and sudden death.

Administration of Carvidelol in dialysis patients with dilated cardiomyopathy was associated with impressive results characterized by decreased left ventricular size, improved ejection fraction, and reduced rates of hospitalization and sudden death.

Erythropoiesis-stimulating agents (ESA)

Several recent studies indicate that treatment of anemia in pre-and postdialysis patients is associated with fewer admissions for heart failure and lower rates of death. However because of the well documented increase in mortality with high hemoglobin (Hb) levels, it is recommended that ESA therapy be initiated when Hb levels fall below 10 g/dL and that dose should be titrated so as not to exceed Hb levels of 12 g/dL.

Adel Berbari, MD, is with the American University of Beirut Medical Center in Beirut, Lebanon.

Policy Update

Policy Board Chair Testifies on ASN's Behalf at Food and Drug Administration Meeting

By Rachel Shaffer

The medical community recently has raised concerns about the Food and Drug Administration's (FDA's) use of Risk Evaluation and Mitigation Strategy (REMS) to ensure the safe use of drugs.

Since 2008, if FDA believes a drug's risks may outweigh its benefits, or that the drug potentially poses serious risks to patients, it mandates that the manufacturer develop a REMS. FDA instituted a REMS for erythropoeisis stimulating agents (ESAs) in February 2010.

In light of concerns that the REMS requirements are burdensome and may be a barrier to accessing needed drugs for some patients, FDA is taking a second look at the REMS program. The agency convened a public hearing on the issue in July. ASN Public Policy Board Chair Thomas Hostetter, MD, FASN, testified on behalf of the American Society of Nephrology.

Roughly 100 REMS exist, but the components of the REMS (such as Medication Guides or monitoring programs) vary by drug. As part of the REMS for ESAs, physicians must provide a five-page Medication Guide about ESAs to all patients receiving the medication—including patients with kidney disease—when an ESA is dispensed. Doctors who give ESAs to patients with cancer must, in addition, train and enroll in the ESA APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs) Oncology Program and document that they discussed the risks of ESAs with each patient prior to the initiation of each new course of ESA therapy.

Hostetter—who served on three panels at the FDA meeting—focused his remarks on the effect of REMS on patients on dialysis. While applauding the goals of REMS in promoting patient safety, Hostetter raised concerns about the Medication Guide's current content balance and sensitivity level.

For example, the ESA Medication Guide begins with the question "What is the most important information I should know about Aranesp?" and the answer "Using Aranesp can lead to death or other serious side effects." (See Figure 1). Many nephrologists are troubled that this strong introductory statement, followed by a detailed review of the risks of ESAs (with scant information on their benefits) may frighten patients away from a medication that is crucial to preserving their vitality and quality of life. Hostetter emphasized to FDA that REMS should present information on the benefits as well as the risks of therapies in a sensitive manner.

The frequency of distribution and review of the Medication Guide with patients—once per month—may also be misguided for this patient population, Hostetter said. Unlike cancer patients, who are treated for a relatively short amount of time, dialysis patients will receive ESAs for the rest of their lives, or until they receive a transplant. Monthly review of the dangers of ESAs may not constitute the best use of time for patients or nephrologists and, over time, may create undue concern about the drugs among some patients.

Hostetter further emphasized that "REMS should be administered on a schedule that best facilitates patient attention to their content, depending on how often the drugs are administered or dosages changed." A less frequent distribution schedule, such as biannually, may be more reasonable for the kidney disease population. Yet, recognizing the importance of dialog between nephrologists and their patients about ESAs, Hostetter said that in the dialysis environment, physicians (or qualified nurse practitioners and physician assistants), should be responsible for administering and reviewing REMS for ESA with patients.

"We are also concerned about how to evaluate the effectiveness of REMS in this group," Hostetter said. It is important that FDA make sure this program is meaningful and effective, but efforts to evaluate the effectiveness of a REMS involving patients—such as a follow-up survey or phone call—should be respectfully designed, ensuring that evaluation efforts do not cause alarm. Patients should also be involved in development and evaluation of any REMS program, Hostetter said.

FDA has yet to finalize its guidance regarding REMS, but will take testimony presented at the July meeting into account. The agency has not proposed expanding the APPRISE program from the oncology to the nephrology arena. ASN will continue to monitor FDA's activity in this area and advocate for decisions that promote informative, sensitive, and safety-conscious programs.

Figure 1. Excerpt from page one of ESA Medication Guide: therapeutic options

MEDICATION GUIDE

Aranesp® (Air-uh-nesp)
(darbepoetin alfa)

Read this Medication Guide before you start Aranesp, each time you refill your prescription, and if you are told by your healthcare provider that there is new information about Aranesp. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Talk with your healthcare provider regularly about the use of Aranesp and ask if there is new information about Aranesp.

What is the most important information I should know about Aranesp?

Using Aranesp can lead to death or other serious side effects.

Proposed Rules Would Lower the Amount of Industry Money that Constitutes a Conflict for Researchers

By Daniel Kochis

A newly proposed rule on conflict of interest in medical research would reduce the monetary amount that qualifies as a conflict for researchers from $10,000 to $5000. Issued by the National Institutes of Health (NIH) in May, the rule is designed to help strengthen the current rules governing conflicts of interest between researchers and industry.

In addition to changing the definition of "significant financial interest" by reducing it to a total of $5000, the rule supports creating a website for public reporting of significant financial interests among researchers and placing increased responsibility on individual institutions to monitor potential conflicts of interest among their researchers.

The relationship between research and industry has always been complex. Industry support is crucial to the success of research. This support, however, must be balanced with the fundamental need for researchers to remain impartial when carrying out their research and interpreting results. Key to the public's trust in the medical profession and confidence in new treatments is this belief in impartiality. NIH grants remain the foremost vehicle for government to help fund medical research. NIH accounts for almost a third of all medical research spending at 27 percent. Industry accounts for the majority of funding at 58 percent (1). The important role NIH plays in funding medical research underscores the significance of this proposed rule.

Before issuing final recommendations, NIH solicited feedback from the research community on its proposals. The American Society of Nephrology (ASN) submitted a comment letter supporting a number of proposals included in the rule. These comments were crafted with the assistance of Thomas Hostetter MD, Dwight McKinney MD, Bruce Molitoris MD, FASN, John R. Sedor, MD, and John Stokes III MD, FASN.

In particular, ASN backs the new definition of significant financial interest. ASN also agrees with new guidelines that expand the definition of significant financial interest to include income from non-higher education nonprofits. ASN further commended the idea to create a public site for reporting significant financial interest. ASN views these changes as reasonable and not overly onerous for researchers.

ASN voiced concern over the burden placed on individual academic institutions to monitor conflict of interest. Placing responsibility largely at a facility level may result in disparate standards across research facilities, potentially to the detriment of researchers at institu-

Journal View

In AASK Patients, ESRD Risk Exceeds Mortality

African American patients with hypertensive nephrosclerosis are more likely to develop end stage renal disease (ESRD) than they are to die or develop cardiovascular disease (CVD), according to data from the African American Study of Kidney Disease and Hypertension (AASK) reported in the *Journal of the American Society of Nephrology*.

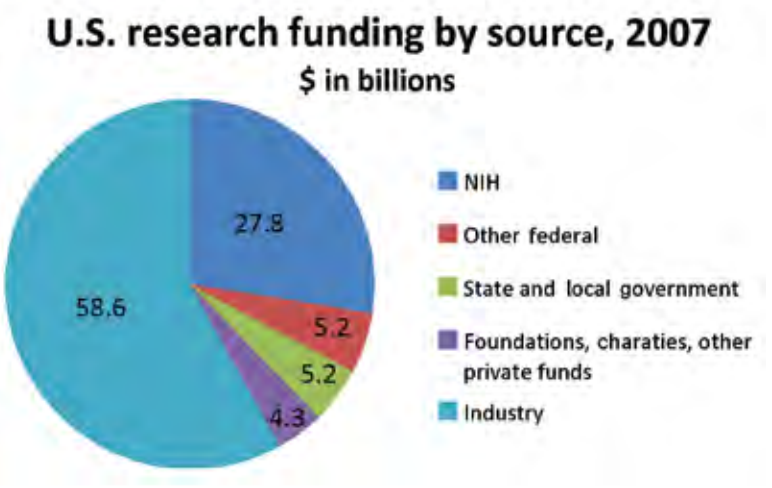
Of 1094 African American patients with hypertensive nephrosclerosis enrolled in AASK, 764 had no events during an initial trial phase, from 1996 to 2001. Of these, 691 enrolled in a subsequent cohort phase, from 2002 through 2007. Eleven-year follow-up data were used to compare the rate of incident ESRD with total or CVD mortality and a composite of CVD death and hospitalization.

There were 59 CVD-related and 118 non-CVD-related deaths during follow-up. The rate of incident ESRD was 3.9/100 patient-years. This compared to total mortality of 2.2/100 patient years, CVD mortality of 0.8/100 patient-years, and a composite CVD outcome rate of 3.2/100 patient-years.

Overall, patients were five times more likely to develop ESRD than to die of CVD. The risk of ESRD exceeded mortality risk across subgroups based on age, sex, income, education, history of CVD, baseline proteinuria, and baseline kidney function.

African Americans with ESRD have lower CVD morbidity and mortality than white patients, but it has been unclear whether a similar racial difference applies to patients with chronic kidney disease. The AASK study provides an opportunity to assess long-term outcomes in African American patients with hypertensive nephrosclerosis and good blood pressure control.

The results suggest that these patients are more likely to have progression to ESRD than death from any cause, death from CVD, or a major CVD event. The findings may lend new insights into the relationship between high blood pressure and kidney disease in African Americans, and into reported racial differences in ESRD. Further study is needed to evaluate possible explanations for the lower cardiovascular mortality in this high-risk minority population [Alves TP, et al. Rate of ESRD exceeds mortality among African Americans with hypertensive nephrosclerosis. *J Am Soc Nephrol* 2010; 21: 1361–1369].



tions that enforce more stringent policies. ASN recommends that NIH develop clear guidelines for enforcement and administration of conflict of interest to help create a level playing field across all institutions nationwide, alleviating institutional differences in enforcement of conflict of interest rules. ASN also recommends NIH keep in mind the administrative burden increased conflict of interest reporting may have on researchers and institutions alike, taking this into consideration when issuing final recommendations.

"Any new conflict of interest guidelines should help institutions educate their faculty and make the rules more uniform, not decrease the amount of research done in universities because of onerous paperwork," said Sedor.

The Society continues to monitor NIH recommendations regarding conflicts of interest to ensure the regulations reflect the best interests of researchers and patients. Read ASN's comment letter and learn more about research-related issues in nephrology on the Society's Medical Research Policy page at http://asn-online.org/policy_and_public_affairs/medical-research.aspx.

Reference

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