

The Role of the Kidney in Heart Failure

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The Normal Relationship of the Heart and Kidney

Because the kidneys receive 20% of cardiac output, heart and kidney function are interdependent. Changes in volume and pressure in the cardiac atria initiate reflexes that alter renal function. Gauer and colleagues were the first to demonstrate that an increase in left atrial pressure was associated with a water diuresis; this effect was shown to be associated with a suppression of the antidiuretic hormone, arginine vasopressin (AVP). This so-called Henry-Gauer reflex is mediated via the vagus nerve to the central source of AVP synthesis and release in the hypothalamo-neurohypophyseal system. Thus, vagotomy

abolishes this atrial-renal reflex.¹ The water diuresis, which has been associated with paroxysmal atrial tachycardia, is probably related to this same reflex.² There is also evidence that atrial transmural pressure exerts an effect on renal sympathetic tone. Specifically, an increase in atrial pressure is associated with a decrease in renal sympathetic activity, thereby attenuating any neurally mediated vasoconstriction of the kidney.³ This atrial-renal reflex would also be expected to dampen any effect of beta-adrenergic stimulation to increase renin release.⁴

Granules had been observed in cardiac atria, but their function was not known. De Bold⁵ wondered whether these granules might contain hormones and proceeded to test this hypothesis. He discovered that rats injected with these granules demonstrated a profound increase in urinary sodium and water excretion. This substance was thus named atrial natriuretic peptide (ANP). In addition to the natriuretic effect, ANP was

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found to exert other properties, including suppression of both the renin-angiotensin-aldosterone system (RAAS) and sympathetic neural activity, as well as being a potent renal and systemic vasodilator. The cardiac ventricles have been found to be the source of another natriuretic peptide termed brain natriuretic peptide (BNP; or B-type natriuretic peptide), since it was first found in the brain. BNP and ANP have similar properties.

The role of BNP to attenuate renal sodium retention secondary to a decrease in systemic arterial pressure was demonstrated by Clavell et al.⁶ Mean arterial pressure was lowered to the same level by either decreasing cardiac function or constricting the thoracic vena cava. Atrial pressure rose with the cardiac, but not the caval, maneuver. Thus, plasma BNP increased with hypotension secondary to decreased cardiac function, but not with caval constriction. Renal sodium retention was significantly greater with the caval constriction despite comparable hypotension. To test whether this was due to the difference in plasma BNP concentrations, the caval animals were administered exogenous BNP to mimic the plasma level observed in the cardiac-mediated hypotension. The sodium excretion typically produced by BNP was blunted in these animals while the hypotensive effect persisted.

The Effect of Central Venous Pressure

Increased right-sided cardiac volume and pressure also can exert effects on the kidney. With the atrial-renal reflexes discussed, the kidney responses tend to lower cardiac-filling pressure by increasing sodium and water excretion. However, a rise in central, and thus renal, venous pressure during increased cardiac preload may actually enhance renal sodium and water retention. Experimental studies have shown that an increase in renal

venous pressure is associated with a rise in interstitial pressure, activation of the RAAS, and a fall in glomerular filtration rate (GFR) and renal sodium retention.^{7,8}

The Effect of Decreased Cardiac Output

In addition to the atrial-renal reflexes and the effects on renal venous pressure, the heart can also affect the kidney by activating high-pressure arterial baroreceptors.⁹⁻¹¹ Arterial stretch baroreceptors are found in the carotid sinus, aortic arch, and afferent arteriole of the glomerulus. Normally, the vagus and glossopharyngeal afferent pathways from these high-pressure receptors inhibit sympathetic outflow from the central nervous system (CNS). With a decrease in stroke volume or a decline in arterial pressure, this CNS inhibition is removed and an increase in sympathetic efferent outflow as well as nonosmotic AVP release occurs. The increase in sympathetic tone stimulates the RAAS via the renal beta-adrenergic pathway.⁴ This neurohumoral stimulation, which results from diminished cardiac function, exerts multiple effects on the kidney. Adrenergic and angiotensin receptors on the proximal tubule epithelium, when stimulated, enhance proximal tubule sodium reabsorption. In addition to these direct effects on sodium balance, the resultant decreased fluid and sodium delivery to the distal nephron also has an effect on urinary sodium excretion. The sodium-retaining effect of aldosterone is only temporary because of the "escape phenomenon." Normally, the expansion of extracellular fluid volume (ECFV) secondary to aldosterone increases GFR, decreases proximal tubule reabsorption, and enhances sodium delivery to the distal nephron, the site of aldosterone activity. This effect, along with the rise in plasma ANP, which occurs with ECFV expansion, overrides the effect

of aldosterone to enhance tubular sodium reabsorption and accounts for aldosterone escape. In contrast, the diminished distal sodium delivery that occurs with neurohumoral activation abolishes the normal aldosterone escape, leading to continued aldosterone-mediated renal sodium retention. Micropuncture studies have also shown that a decrease in renal arterial perfusion pressure, as may occur with a decrease in cardiac output, causes enhanced proximal tubule sodium reabsorption.⁸

As with aldosterone, the site of action of natriuretic peptides is also in the distal nephron—namely the collecting duct. Thus, the natriuretic response of these peptides is also dependent on distal sodium delivery, and the resistance to the natriuretic response of ANP and BNP in cardiac failure appears to be secondary to the neurohumoral-mediated diminished sodium delivery to the collecting duct site of their action.

There are numerous pathways, therefore, whereby the heart can affect the function of the normal kidney. In fact, when this occurs, either acutely or chronically, the term *cardiorenal syndrome* has been used in clinical medicine.¹¹ This is different than when acute or chronic renal parenchymal disease is associated with increased cardiovascular complications, which can most appropriately be termed *renocardiac syndrome*. The experimental information described here can be used to understand the effects on kidney function that occur with cardiovascular disease. We now focus on how abnormal cardiac function can affect kidney function in human disease.

Kidney Function with Congestive Heart Failure

In patients with asymptomatic or symptomatic congestive heart failure (CHF), a mild or

moderate decrease in kidney function correlates with a highly significant increase in morbidity and mortality.^{12,15} Reduced kidney function after an acute myocardial infarction is also associated with increased mortality.¹⁵ Minimal increases in serum creatinine (> 0.5 mg/dL) within 48 hours after cardiothoracic surgery in patients with baseline serum creatinine < 1.5 mg/dL was associated with an 10-fold increase in 30-day mortality independent of other variables.¹⁴ There has been considerable discussion as to whether the worsening of renal function in CHF patients is merely a marker for poor outcomes or actually a pathogenetic factor in causing the progression of functional cardiac dysfunction.

The Role of Neurohumoral Axis in Congestive Heart Failure

The seeming paradox of increased blood volume with renal sodium and water retention in cardiac failure has been explained by the body fluid volume regulation hypothesis.^{9,10,15} This hypothesis proposes that the kidney does not respond to changes in total blood volume but rather responds to what has been termed *effective arterial blood volume*. In general terms, approximately 85% of circulating blood volume is in the low-pressure venous side of the circulation, whereas only 15% is in the high-pressure arterial circulation. The integrity of the arterial circulation depends on cardiac output and systemic vascular resistance and is modulated by arterial stretch baroreceptors in the carotid sinus, aortic arch, and afferent arteriole of the glomerulus. Thus, despite an increase in total blood volume, arterial underfilling may develop secondary to a decrease in cardiac output in heart failure or decreased systemic vascular resistance in high-output heart failure. With arterial underfilling secondary to either condition, arterial baroreceptor-mediated activation of the neurohumoral

axis occurs. The resultant increase in RAAS leads to sodium retention, and the increase in the nonosmotic release of AVP is associated with water retention and hyponatremia in advanced left ventricular failure.

Considerable evidence shows that renal activation of the RAAS, which occurs with diminished cardiac function, contributes to increased morbidity and mortality. Angiotensin II activates the sympathetic nervous system (SNS), and mortality in heart failure correlates both with increased plasma renin activity¹⁶ and with norepinephrine concentrations.¹⁷ Angiotensin II also is known to cause cardiac remodeling, a known pathogenetic factor in CHF.¹⁸ Even though chymases, rather than angiotensin-converting enzyme (ACE), are known primarily to convert angiotensin I to the bioactive angiotensin II in the heart, ACE inhibition has been shown in prospective randomized studies to improve left ventricular function, attenuate left ventricular remodeling, and increase survival in patients with CHF.¹⁹ Some of these beneficial effects with ACE inhibition may be due to increased bradykinin, because bradykinin degradation is decreased with ACE inhibition.^{20,21} Blockade of angiotensin-induced AT1 receptor activation inhibits synthesis of tumor necrosis factor- α , inducible nitric oxide, free radical formation, and transforming growth factor- β , all of which are stimulated by angiotensin II and are deleterious to the heart.²² Similarly, beta-adrenergic blockade in randomized studies with controlled-release metoprolol²³ and carvedilol²⁴ has been shown to improve survival in patients with CHF.

Angiotensin II and the SNS, which are activated by a decrease in cardiac stroke volume, increase systemic vascular resistance and maintain arterial pressure. However, the trade-offs of this response are not only the effects on the kidney relating to sodium and water retention, failure to escape from the

sodium-retaining effect of aldosterone, and resistance to the natriuretic effect of ANP and BNP but also the increase in cardiac afterload. An increase in cardiac afterload in an already ischemic heart in CHF patients can further impair cardiac function.

The Specific Role of Aldosterone in Congestive Heart Failure

The renal activation of the renin-angiotensin system secondary to impaired cardiac function is associated with increased plasma aldosterone concentration, which is also related to increased mortality in CHF patients.¹⁶ The Randomized Aldactone (spironolactone) Evaluation Study (RALES) used doses (25–50 mg/24 h) of the aldosterone antagonist, spironolactone, which did not alter urinary sodium excretion.^{25,26} The results demonstrated improved survival in CHF patients, indicating a protective effect of aldosterone, which has an antifibrotic effect on the heart and blood vessels. There are, however, results that also suggest that secondary hyperaldosteronism is an important renal sodium-retaining mechanism in patients with CHF.^{27,28} A lowering of plasma aldosterone with ACE inhibition in CHF, however, may not cause a natriuresis for at least 2 reasons. First, a decrease in angiotensin II with ACE inhibitor diminishes mean arterial pressure, and thus lowers renal perfusion pressure, which may obscure the expected natriuresis normally associated with decreased plasma aldosterone. Second, in 30% to 40% of patients receiving an ACE inhibitor, plasma aldosterone will initially decrease but later the plasma aldosterone level will increase to baseline. This phenomenon, termed *aldosterone "break-through,"* can have important clinical consequences given aldosterone's profibrotic actions on diverse organ systems, including the heart and kidney, as well as the hormone's sodium-retaining effect.²⁹

Diagnosis and Prognosis of Cardiorenal Syndrome

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The term *cardiorenal syndrome* often refers to a condition in which renal impairment occurs as a result of cardiac dysfunction.¹ This view is supported by the observation that a previously impaired renal function improves after a cardiac assist device is implanted in a patient with end-stage heart failure (HF).² The expression “cardiorenal syndrome” has also been used to describe the negative effects of renal disorders on heart structure and function.³ Thus, although the term *cardiorenal syndrome* is loosely applied to many pathological interactions between the heart and the kidney, until recently a comprehensive definition was lacking. To be inclusive of the damage/dysfunction produced in either the heart or the kidney by an acute or chronic disease of the other organ, car-

diorenal syndrome should be classified according to whether the impairment of each organ is primary or secondary, or whether abnormal heart and kidney functions occur simultaneously as a result of a systemic disease.⁴ For example, acute HF decompensation can cause both acute renal injury and chronic kidney disease (CKD): a decreased cardiac output is associated with renal arterial underfilling and increased venous pressure, which, in turn, result in a reduced glomerular filtration rate (GFR).⁵ Activation of the renin-angiotensin-aldosterone system (RAAS), initially aimed at restoring GFR, eventually leads to increased renal expression of endothelin 1 (ET-1), a potent proinflammatory and profibrotic vasoconstrictor peptide known to mediate acute and chronic kidney injury.⁴

In chronic HF, increased sympathetic nervous system and RAAS activity augment oxidative stress to the kidneys and impair action of nitric oxide on the vascular endo-

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thelium.⁵ Activation of the RAAS, which increases production of angiotensin II and aldosterone within the kidney, is a key factor in the development of end-organ damage in the heart, vasculature, and kidneys.⁶ Chronic HF is often complicated by anemia, known to independently worsen hemodynamic and clinical outcomes, and by the release of inflammatory cytokines including tumor necrosis factor- α (TNF- α), interleukin 1 (IL-1), and interleukin 6 (IL-6). This inflammation leads to gradual toxic injury to renal cells and eventually to chronic kidney damage and functional loss.⁴

Conversely, acute kidney injury (AKI) can provoke cardiac failure. Models of post-ischemic renal injury have demonstrated the intrarenal accumulation of neutrophils, macrophages/monocytes, and lymphocytes and increased circulating levels of inflammatory cytokines, which can impair cardiac contractility and trigger myocytes apoptosis.⁴

CKD independently increases the risk of cardiovascular disease by promoting myocardial hypertrophy, coronary atherosclerosis, and fluid overload. Anemia, advanced glycation end-products (AGEs), abnormal calcium-phosphate metabolism, nutritional factors, extracellular fluid accumulation, inflammation, insulin resistance, hyperhomocysteinemia, oxidative stress, and dyslipidemia have all been implicated in the amplification of cardiovascular morbidity by CKD.⁵ In addition, by inhibiting Na-K-ATPase, uremic toxins may increase contractile force and impair relaxation of cardiac myocytes, thus contributing to the diastolic dysfunction commonly encountered in patients with CKD.⁴

Finally, highly prevalent conditions, such as diabetes and hypertension, and less common ones, including autoimmune diseases, amyloidosis, pulmonary arterial hypertension, and sepsis, can simultaneously damage the heart and kidneys.^{4,5}

This chapter will examine the methods currently used to diagnose the presence of renal dysfunction in patients with cardiovascular disease (CVD), describe a newly proposed classification of cardiorenal syndrome, summarize the evidence for the impact of renal disease on cardiovascular outcomes, and describe the data showing that renal dysfunction worsens the outcomes of HF patients.

Diagnosis by Primary Organ Dysfunction and Acuity of Events

Although generally defined as a condition characterized by the initiation and/or progression of renal insufficiency secondary to HF, the term *cardiorenal syndrome* is also used to describe the negative effects of reduced renal function on the cardiovascular system.⁴ The direct and indirect effects of each dysfunctional organ can initiate and perpetuate the combined disorder of the 2 organs through complex neurohormonal feedback mechanisms. Consequently the subdivision of cardiorenal syndrome into 5 different subtypes may facilitate care of individual patients (Table 3.1).

Type 1 cardiorenal syndrome (acute cardiorenal syndrome) defines a rapid deterioration in cardiac function, which produces AKI. Regardless of whether acute HF presents as hypertensive pulmonary edema with preserved left ventricular (LV) systolic function, exacerbation of chronic HF, cardiogenic shock, or predominantly right ventricular (RV) failure, premorbid CKD is common and increases the risk of AKI.^{7,8} Severity of AKI is greater in patients with impaired than in those with preserved LV systolic function, and it occurs in more than 70% of patients with cardiogenic shock.⁷ As discussed later

Table 3.1: Cardiorenal Syndrome

Type 1: acute cardiorenal syndrome

Abrupt worsening of cardiac function (eg, acute cardiogenic shock, or ADHF) leading to acute kidney injury

Type 2: chronic cardiorenal syndrome

Chronic abnormalities in cardiac function (eg, chronic HF) causing progressive and potentially permanent chronic kidney disease

Type 3: acute renocardiac syndrome

Abrupt worsening of renal function (eg, acute kidney ischemia or glomerulonephritis) causing acute cardiac disorders (eg, HF, arrhythmia, ischemia)

Type 4: chronic renocardiac syndrome

Chronic kidney disease (eg, chronic glomerular or interstitial disease) contributing to decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events

Type 5: secondary cardiorenal syndrome

Systemic conditions (eg, diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

Adapted from Ronco C, Haapio M, House AA: Cardiorenal syndrome. *J Am Coll Cardiol*. 2008; 52:1527–1539. With permission from Elsevier.

in this chapter, renal dysfunction consistently and independently predicts 1-year mortality in patients with acute decompensated heart failure (ADHF), possibly because an acute decline in renal function accelerates progression of CVD through activation of inflammatory pathways.⁵ Key concerns regarding AKI are whether it represents inadequate renal perfusion due to either a low

cardiac output (CO) and/or marked increase in central venous pressure (CVP), decreased diuretic responsiveness, or intravascular volume depletion from overzealous diuresis.³ Accurate diagnosis and appropriate treatment of type 1 cardiorenal syndrome may require measurement of CO and CVP.⁴ In addition, renal function and potassium levels should be closely monitored to minimize avoidance of lifesaving medications such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and aldosterone blockers.⁴ However, initiation of beta-blockers, particularly atenolol and sotalol, which undergo renal excretion, should be deferred until hemodynamic stability is achieved.⁴ Kidney function should be closely monitored also in patients with acute myocardial infarction (AMI), and in those undergoing cardiac surgery, percutaneous coronary intervention (PCI), or radiocontrast cardiac imaging, because in these settings an increase in serum creatinine signals the onset of AKI, which, in turn, may accelerate cardiovascular injury through activation of neurohormonal, immunological, and inflammatory pathways.^{3–5} As discussed later in this chapter, even a modest increase in serum creatinine (> 0.3 mg/dL) is an independent predictor of unfavorable cardiovascular outcomes. Attempts to attenuate renal damage are largely futile because renal function markers such as serum creatinine rise only after AKI has occurred.⁴ However, the discovery of novel AKI biomarkers may permit an earlier diagnosis of cardiorenal syndrome (Table 3.2). The use of a complementary deoxyribonucleic acid (DNA) microarray has identified a subset of genes whose expression is up-regulated within the first few hours after the onset of AKI.⁹ Urine and serum neutrophil gelatinase-associated lipocalin (NGAL) levels are early predictors of AKI after use of radiocontrast and cardiac surgery. In critically ill patients elevation of

**Table 3.2 Protein Biomarkers
for the Early Detection of Acute Kidney Injury**

Biomarker	Associated Injury
Cystatin C	Proximal tubule injury
KIM-1	Ischemia and nephrotoxins
NGAL (lipocalin)	Ischemia and nephrotoxins
NHE3	Ischemia, pre-renal, post-renal AKI
Cytokines (IL-6, IL-8, IL-18)	Toxic, delayed graft function
Actin-actin depolymerizing F	Ischemia and delayed graft function
α -GST	Proximal tubule injury, acute rejection
II-GST	Distal tubule injury, acute rejection
L-FABP	Ischemia and nephrotoxins
Netrin-1	Ischemia and nephrotoxins, sepsis
Keratin-derived chemokine	Ischemia and delayed graft function

GST = glutathione S-transferase; IL = interleukin; KIM = kidney injury molecule; L-FABP = L-type fatty acid binding protein; NGAL = neutrophil gelatinase-associated lipocalin; NHE = sodium-hydrogen exchanger. Ronco C, Haapio M, House AA. Cardiorenal syndrome. *J Am Coll Cardiol.* 2008;52:1527–1539. With permission from Elsevier.

NGAL levels precedes that of serum creatinine by 48 to 72 hours.¹⁰ Cystatin C also predicts AKI and the requirement for renal replacement therapy earlier than serum creatinine elevation¹¹ (Figure 3.1). After cardiac surgery both cystatin C and NGAL predicted renal damage at 12 hours, but NGAL was superior to cystatin C at earlier time points.⁴ Kidney injury molecule 1, a protein detectable in the urine after proximal tubular cells injury, may be highly specific for ischemic AKI. Biomarkers such as N-acetyl- β -(D)glucosaminidase, IL-18, and others have been evaluated for their ability to detect AKI and CKD progression. Use of a “panel” of biomarkers that includes several serum and urinary molecules may ultimately permit

detection of AKI before irreversible renal damage has occurred.⁴

Type 2 cardiorenal syndrome (chronic cardiorenal syndrome) refers to progressive CKD occurring in approximately 25% of HF patients.¹² Its presence and worsening renal function (WRF) in HF patients are consistently associated with adverse outcomes, as discussed in detail later in this chapter. Chronic HF may be associated with longstanding renal hypoperfusion often aggravated by co-existing micro- and macrovascular disease.⁴ Other causes of the onset and progression of renal dysfunction in chronic HF include neurohormonal activation; resistance to natriuretic peptides; iatrogenic hypovolemia and hypotension and down-regulation of

The Use of ACE Inhibitors and Angiotensin Receptor Blockers in Patients with Coexistent Renal Disease and Heart Failure

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Compounds that interfere with activity of the renin-angiotensin-aldosterone system (RAAS) have been established as effective in the treatment of hypertension, as well as a variety of end-organ diseases including proteinuric chronic kidney disease (CKD), heart failure (HF), and stroke. Inhibitors of the RAAS either quantitatively reduce angiotensin II concentrations (angiotensin-converting enzyme [ACE] inhibitors and direct renin inhibitors [DRIs]) or limit the activity of angiotensin II at the receptor level (angiotensin receptor blockers [ARBs]). Although RAAS inhibitors typically increase renal blood flow (RBF) and sodium (Na⁺) excretion rates in HF and reduce the rate at which renal injury progresses in CKD, their use can also be coupled to a syndrome of “functional

renal insufficiency” and/or hyperkalemia. This form of acute kidney injury (AKI) most commonly develops shortly after beginning ACE inhibitor, ARB, or DRI therapy but can occur at any time in the course of chronic therapy, even in the absence of obvious predisposing factors.^{1,2}

Acute kidney injury with RAAS inhibitors typically occurs when renal perfusion pressure cannot be maintained because of a substantial decrease in mean arterial pressure (MAP) or when the glomerular filtration rate (GFR) is overly dependent on the postglomerular efferent arteriolar constricting effect of angiotensin II.^{3,4} Conditions that predict an adverse renal hemodynamic effect of RAAS inhibitors in patients with HF are preexisting low MAP values (typically < 60–65 mm Hg) and/or extracellular fluid volume (ECFV) depletion to the extent that the lowered cardiac filling pressures lead to a reduction in cardiac output. Glomerular filtration rate is heavily dependent on angiotensin II during

ECFV depletion, high-grade bilateral renal artery stenosis, stenosis of a dominant or single kidney (as in a renal transplant recipient), and/or extensive microvascular renal disease. Understanding the pathophysiological mechanisms and the common risk factors for RAAS inhibitor-induced functional AKI is of some particular importance, because preventive approaches for AKI exist, and when such strategies are brought into play, they may allow for use of these compounds in a less restrictive fashion.^{1,4}

Systemic/Renal Effects of Angiotensin II Pertinent to Heart Failure

Under usual physiological conditions, renal vascular resistance is coupled to the process of renal autoregulation, which, in turn, is influenced by local and systemically produced angiotensin II (as well as sympathetic nervous system [SNS] activity and other neurohumoral systems). As renal perfusion pressure falls in HF, both the SNS and the RAAS activate and generous amounts of angiotensin II are produced. Angiotensin II so generated has a predominant constricting effect on the postglomerular circulation, and this vascular action increases upstream glomerular capillary pressures, thereby maintaining glomerular filtration despite the otherwise reduced renal perfusion pressures. Angiotensin II also promotes proximal tubular Na⁺ reabsorption and acts as a central dipsogen (ie, an agent that induces thirst).^{5,6} These latter 2 aspects of angiotensin II effect contribute to the occurrence of hyponatremia in untreated HF. Administration of a RAAS inhibitor increases serum Na⁺ concentrations in the HF patient with

hyponatremia unless the GFR has significantly declined with this therapy.⁷

Benefits of Long-Term Use of ACE Inhibitors and Angiotensin Receptor Blockers in Heart Failure

In patients with both symptomatic and asymptomatic myocardial dysfunction, long-term administration of ACE inhibitors reduces symptoms from HF, as well as the morbidity and mortality that accompanies this disease.⁸ This beneficial effect of ACE inhibitors was recognized as early as 1984 and more recently has been shown to be the case with ARB therapy. ACE inhibitor and/or ARB therapy favorably affects the progression rate of a number of proteinuric and nonproteinuric renal diseases (that are often associated with HF development), which results in their being commonly used in the patient with CKD.⁹ The beneficial effects of ACE inhibitor and ARB therapy in chronic nephropathies (with or without HF) are related to their hemodynamic actions as well as a wide range of neurohumoral, cellular, and vascular actions. This positive effect of ACE inhibitor and/or ARB therapy in chronic nephropathies is marked by a transient/reversible fall in the GFR in the order of 10% to 20%.¹⁰ In the patient with early stage HF and a reduced GFR (either of a primary or a secondary nature) given ACE inhibitor and/or ARB therapy, a similar degree of change in the GFR is an anticipated treatment consequence. Alternatively, in the more advanced stages of HF, wherein GFR is reduced in tandem with the HF state, the change in GFR with either ACE inhibitor and/or ARB therapy can be dramatic and therapy limiting.¹

Renal Function and the Heart

The issue of change in renal function with ACE inhibitor and/or ARB therapy in patients with coexistent renal disease and HF is a confusing one and often requires careful deciphering based on the definitional terminology in use. Acute kidney injury (functional renal insufficiency) in HF is defined as a sudden reduction in renal function, usually heralded by a not insignificant rise in serum creatinine concentration. Although no precise increase in serum creatinine defines AKI, an increase of 0.5 mg/dL (44 μ mol/L) if the serum creatinine was initially < 2.0 mg/dL, or 1.0 mg/dL if the serum creatinine was above 2.0 mg/dL, was offered as a practical working definition in an American Heart Association scientific statement published in 2001.¹ Since that time, there has been a revival of interest in how best to define a change in renal function in HF (with or without ACE inhibitor therapy) with attention directed to novel biomarkers other than creatinine and use of estimated change in GFR (eGFR) rather than change in serum creatinine.¹¹

The fast-changing nature of this field is best exemplified in the area of acute decompensated heart failure (ADHF), where functional renal insufficiency is a not infrequent occurrence impacting overall prognosis. Therein, the term *worsening renal function* (WRF) has been employed to describe a treatment-related rise in serum creatinine with increases of ≥ 0.3 mg/dL being of short- and long-term prognostic significance.¹² WRF, if sufficiently extreme and accompanied by features such as diuretic resistance and anemia, has been termed *cardiorenal syndrome*.¹⁵ Although the expression has quickly become a term of convenience used to mark a change in renal function in the HF patient, there has not been a consistent meaning to its use.

A recent classification of cardiorenal syndrome into categories, albeit arbitrary, provides needed perspective on the sorting of the confusing bidirectional nature of kidney-heart interactions. Five subtypes of cardiorenal syndrome have been proposed, which reflect the temporal nature of the organ interactions as well as the primary and secondary pathology of the kidney-heart exchange.

- **Type 1 cardiorenal syndrome** (acute cardiorenal syndrome) reflects an abrupt worsening of cardiac function, such as ADHF, leading to acute kidney injury.
- **Type 2 cardiorenal syndrome** (chronic cardiorenal syndrome) describes long-standing abnormalities in cardiac function, such as chronic advanced-stage HF causing progressive and permanent CKD.
- **Type 3 cardiorenal syndrome** (acute renocardiac syndrome) reflects an abrupt worsening of renal function, such as with the nephrotic syndrome, bringing about an acute cardiac disorder, such as HF or coronary ischemia.
- **Type 4 cardiorenal syndrome** (chronic renocardiac syndrome) describes CKD of any origin contributing to structural and functional cardiac abnormalities and an amplified risk of cardiovascular events.
- **Type 5 cardiorenal syndrome** (secondary cardiorenal syndrome) is a systemic condition, such as sepsis, leading to both cardiac and renal dysfunction.¹⁵

Acute Renal Failure Due to ACE Inhibitor or Angiotensin Receptor Blocker Therapy

The frequency with which renal function changes in HF patients treated chronically with ACE inhibitors has been reported in several studies. In the Studies of Left Ventricular Dysfunction (SOLVD) trials, 3379 patients were randomly assigned to enalapril (median follow-up of 974 days) and 3379 patients randomly assigned to placebo (mean follow-up of 967 days). Decreased renal function was defined as a rise in serum creatinine of ≥ 0.5 mg/dL ($44\text{-}\mu\text{mol/L}$) above baseline. Sixteen percent of patients randomly assigned to enalapril had a decrease in renal function compared with 12% in the placebo controls, indicating a 4% (16% minus 12%) greater likelihood of an episode of decreased renal function with ACE inhibitor therapy. By multivariate analysis, in both the placebo and enalapril groups, older age, diuretic therapy, and diabetes were associated with a greater likelihood of a negative renal function change, whereas beta-blocker therapy and a higher ejection fraction were renoprotective in all patients irrespective of therapy.¹⁴

The frequency with which renal function changes in both the enalapril and placebo-treated limbs of SOLVD offers at best a rough approximation of what can be expected in trials lasting several months or longer. As such, the variables that might increase the frequency with which renal function deteriorates include (1) what change in serum creatinine is defined as being a "renal" event, (2) higher administered doses of either an ACE inhibitor and/or an ARB, and (3) the frequency of sampling taken to detect a change in renal function, concomitant medications

in use (concurrent beta-blocker use affords some renoprotection), and/or whether a predominantly renally or renally/hepatically cleared RAAS inhibitor is being used.^{1,15}

Renal function can deteriorate suddenly when RAAS inhibitor therapy is first begun, or it can acutely change in patients receiving chronic therapy particularly in patients with systolic HF and a low pretreatment MAP value. In either instance there is typically a $> 50\%$ increase in the serum creatinine value. Chronic RAAS inhibitor therapy in the HF patient presents a different set of circumstances; therein, a small change ($< 30\%$) in serum creatinine values often marks the initiation of therapy. Intercurrent events, such as dehydration and/or hypotension, may accentuate the unfavorable renal hemodynamic effects of RAAS inhibitors, with the result being a significant additional decline in function. In the patient receiving chronic RAAS inhibitor therapy, a change in renal function, as assessed by serum creatinine values, is a poor barometer of renal function. It should also be appreciated that situations exist in which a rise in creatinine occurs without a realized change in GFR. Such is the case when trimethoprim (a component of Bactrim) or cimetidine is administered. Both of these compounds are organic cations, known to compete with creatinine for its tubular secretion, and therein limit its utility as an effective marker of renal function.^{16,17}

In most patients who experience AKI with RAAS inhibitor therapy, one or more of 4 mechanisms are typically implicated. First and most importantly, if MAP falls to levels that cannot maintain renal perfusion and/or that provoke substantial reflex renal sympathetic nerve activity, renal function can be expected to decline under such circumstances.¹⁸⁻²⁰ In addition to triggering a sudden and

Practical Management of Cardiorenal Syndrome

A Patient-Centered Approach

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The Acute Decompensated Heart Failure National Registry (ADHERE) study cast a bright spotlight on the effect of renal dysfunction on patients admitted with heart failure (HF). Two of the 3 most important predictors of mortality were markers of renal function blood urea nitrogen (BUN) and creatinine. Coupled with a systolic blood pressure < 115 mm Hg, significant renal dysfunction was associated with a 10-fold increase in mortality compared with those with more normal renal function and blood pressure (2.3% vs 22.5%).¹ These disturbing data can be viewed another way, however; 80% of these high-risk patients survive to hospital discharge. So renal dysfunction in HF is not necessarily a death sentence. It can be managed successfully in most patients.

As can be seen from the preceding chapters there are multiple mechanisms for the development of cardiorenal syndrome (Table 16.1). Therefore, the therapy for cardiorenal syndrome cannot be standardized; it must be individualized to address the unique set of problems for the patient at hand.² That said, a systemic approach to discover the particular cardiovascular derangement is mandatory for 2 reasons:

1. In many instances cardiorenal syndrome is reversible if the immediate cause can be identified and addressed.
2. The appearance of cardiorenal syndrome can be a true medical emergency; a precious window of opportunity may be missed and appropriate therapy can become unsuitable if renal dysfunction progresses to multiorgan failure.

What follows is one approach for the patient with cardiorenal syndrome. Once

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Table 16.1: Potential Causes of Cardiorenal Syndrome

Impaired Renal Perfusion

- Hypovolemia (reduced filling pressures resulting in decreased CO)
- Cardiogenic shock (reduced CO with low systemic blood pressure; usually normal systemic vascular resistance)
- Vasodilatory shock (reduced systemic blood pressure with normal or near normal CO; significant reduction in systemic vascular resistance)
- Reduced CO due to neurohormonal activation and greatly increased afterload; significant increase in systemic vascular resistance
- Reduced renal perfusion due to high central venous pressures
- Renal artery stenosis

Intrinsic Renal Disease

- Longstanding renal dysfunction due to diabetes mellitus, hypertension, etc
- Diuretic resistance

the physiologic derangement is understood (when possible), then appropriate therapy can be instituted.

Causes of Cardiorenal Syndrome

Although cardiorenal syndrome is far from completely understood, several key features have been identified.³ Significant reduction in renal perfusion will impair renal performance and severe HF provides a milieu in which this can occur. The kidney can function adequately across a wide range of car-

diac outputs but when cardiac index falls below 1.5 L/min/m² then renal function declines.⁴ Several distinct mechanisms can impair cardiac output (CO) in HF including hypovolemia (reduced preload), reduced contractility, or a marked increase in afterload. Renal perfusion is also reduced when central venous pressure is markedly elevated. Firth and colleagues⁵ demonstrated this elegantly in an animal model in 1988. Central venous pressures > 20 mm Hg resulted in a marked decline in GFR, which was reversed when pressures were reduced. Mullens and colleagues⁶ also reported that an elevated right atrial pressure was strongly predictive of renal dysfunction in those with advanced HF. Systemic hypotension may also lead to reduced renal function. Again, this can be multifactorial including hypovolemic shock, cardiogenic shock due to a marked reduction in cardiac performance, or vasodilatory shock with relatively preserved CO but inappropriate peripheral vasodilation.⁷

Comorbidities are common in HF patients and may result in intrinsic renal disease independent of, but contributing to, the HF syndrome. In the ADHERE database both diabetes and hypertension were extremely common, 73% and 44%, respectively.⁸ In addition over 60% had at least moderate kidney injury as defined by the Modification of Diet in Renal Disease equation.⁹ Loss of renal function can result in salt and water retention, which can lead to acute HF decompensation. Therapies that improve CO such as inotropes in patients with primarily renal disease are counterproductive in that the CO is already normal and exposes them to the risks of inotropes such as arrhythmias and myocardial ischemia. Chronic use of diuretics can also result in hypertrophy of the distal tubule cells in the nephron, which may increase reabsorption of salt and water resulting in diuretic resistance, another manifestation of cardiorenal syndrome.¹⁰

Management of the Patient with Acute Cardiorenal Syndrome

Because of the many potential etiologies of cardiorenal syndrome and potential treatments, which may be diametrically opposed, a systematic approach to the HF patient presenting with worsening renal function (WRF) is critical. To focus this evaluation 5 key questions must be answered about the patient at hand.

1. What is the fluid status of the patient; is hypovolemia present?
2. Is there systemic hypotension (systolic blood pressure < 80 mm Hg)?
3. What is the cardiac output?
4. Is the central venous pressure markedly elevated?
5. Is there a history of, or evidence for, intrinsic renal disease?

Evaluation of volume status and the early recognition of hypovolemia is important because intercurrent gastrointestinal illness and iatrogenic volume depletion are common yet rapidly correctable. A focused history and physical examination that look for postural blood pressure changes, flat neck veins and absence of rales, and a third heart sound should be adequate to identify most cases of hypovolemia. When the fluid status is in doubt, then a limited echocardiogram can often resolve the issue. Vigorous collapse of the inferior vena cava during respiration, a transmitral E wave < the A wave, and an E wave deceleration time > 200 milliseconds strongly suggests low filling pressures in HF with WRF.¹¹ The recognition of hypovolemia is critical because rapid volume replacement of 500 to 1000 cc of normal saline can improve CO by restoring normal preload, and hence blood pressure and renal

perfusion. Hemodynamic monitoring to determine volume status may be necessary in some circumstances when uncertainty remains (Table 16.2).

Once hypovolemia has been ruled out or corrected, then systolic hypotension should be addressed. Clearly, the lower the systolic blood pressure the more urgently this should be corrected if renal perfusion is to be restored before irreversible damage occurs. In those with less severe hypotension, blood pressure may be restored with dobutamine if there is a history of severe left ventricular (LV) dysfunction. Profound hypotension may require pressor support with norepinephrine and/or epinephrine. The appearance of cardiorenal syndrome coupled with hypotension is a true medical emergency that requires rapid action but also hemodynamic data to address the underlying cardiovascular abnormality. Knowledge of the CO is very useful to tailor therapy to the individual patient. The ESCAPE trial did not show a benefit with hemodynamic monitoring of patients, however, very few patients in the trial had severe renal dysfunction (average creatinine 1.5 mg/dL, BUN 34 mg/dL).¹² Knowing the CO can be important for decision making for several reasons. When the cardiac index is < 1.5 L/min/m² then renal function is difficult to maintain. The use of dobutamine or milrinone in this instance can rapidly improve renal function and stabilize the patient. The resolution of renal dysfunction by improving CO with inotropes demonstrates adequate renal reserve and confirms a cardiac basis for cardiorenal syndrome.

The use of dopamine in cardiorenal syndrome has been the subject of much debate. For a long time low-dose dopamine was given to improve renal blood flow.¹⁵ Randomized trials in acute renal dysfunction due to acute tubular necrosis, however, did not show benefit.¹⁴ However, a study by