Role of Diminished Renal Function in Cardiovascular Mortality
Marker or Pathogenetic Factor?
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The interactions between the heart and the kidney recently have been the focus of intense interest because of epidemiological evidence indicating that even mild deterioration of renal function is an important risk factor for poor outcome in patients with congestive heart failure, myocardial infarction, and cardiovascular surgery. Kidney function deterioration may be a consequence of cardiac and baroreceptor dysfunction or may be primarily caused by intrinsic kidney disease. This review provides a comprehensive analysis of the role of the kidney not only as a marker but also as a pathogenetic factor in cardiorenal syndromes, whether primary heart or primary kidney disease or both are the initiators of the subsequent pathophysiological events. (J Am Coll Cardiol 2006;47:1–8) © 2006 by the American College of Cardiology Foundation

Mild or moderate decreases in renal function have been shown to correlate with significant morbidity and mortality in patients with asymptomatic and symptomatic congestive heart failure (CHF) (1–3), those with myocardial infarction (4), and those undergoing cardiovascular surgery (5). Also, patients with mild chronic renal insufficiency are known to have a significant increase in cardiovascular morbidity and mortality (6,7). However, the mechanisms whereby even mild deterioration of renal function has been found to be a major cardiovascular risk factor are not known. One possibility is that cardiac pump failure may secondarily lead to diminished renal function, and thus early renal failure may only be a marker of impaired cardiac function. Alternatively, even mild or moderate renal dysfunction may also be a pathogenetic factor in causing the progression of functional cardiac deterioration. The potential mechanisms whereby even mild renal dysfunction could be an important contributor to the progression of cardiac disease and cardiovascular mortality are the focus of this review.

KIDNEY FUNCTION AS A RISK FACTOR FOR CHF
A major role of the kidney is the regulation of extracellular fluid (ECF) volume (8). Minor abnormalities in kidney function can impair this capacity to maintain ECF volume within the normal range. In this regard, there are considerable data that indicate that the initiating event in the pathogenesis of essential hypertension is renal sodium retention, which occurs in the presence of apparent normal kidney function (9). In this regard, the hallmark of CHF is renal sodium and water retention. Thus, the use of loop diuretics in CHF patients with dyspnea and shortness of breath is standard therapy. In patients with CHF, diuretics may induce a natriuresis, decrease ECF volume, and provide symptomatic relief; however, cardiac function generally remains stable or decreases depending on the patient’s Frank-Starling curve. If the diuretic-induced natriuresis decreases cardiac pre-load to an extent that diminishes cardiac index, the blood urea nitrogen and serum creatinine levels may increase and cause the clinician to discontinue or decrease the dose of the loop diuretic (10). There are, however, several mechanisms whereby persistent volume overload may lead to progression of heart failure (HF).

Cardiac dilation in CHF. Expansion of ECF can increase cardiac pre-load and lead to cardiac dilation, which can have a deleterious effect on cardiac function. The myocardial remodeling that occurs with cardiac dilation can increase oxygen demand and create a situation of relative myocardial ischemia. Cardiac dilation can also cause functional mitral insufficiency, which may contribute to pulmonary hypertension and impair left and right ventricular function. In early CHF, ventricular dilation is associated with an increase in brain natriuretic peptide (BNP), which may facilitate maintenance of sodium balance and suppress the renin-angiotensin-aldosterone system. Exogenous BNP has also been shown to decrease cardiac pre-load (11), diminish cardiac fibrosis (12), and enhance the diuretic effect of furosemide (13). In patients with more advanced CHF, the effect of natriuretic peptides may be blunted (14) as a result of decreased renal perfusion pressure and diminished sodium delivery to the distal nephron site of BNP action.

Increased left ventricular (LV) mass index in CHF. Volume overload and increased cardiac pre-load can increase transmural myocardial pressure and increase LV mass index. Left ventricular hypertrophy is a major cardiovascular risk
factor with increased mortality relating to systolic and/or diastolic dysfunction, arrhythmias, and sudden death. Because the hypertrophied myocardium has a relative reduction in capillary density, an increase in ischemic events, including angina and infarction, also occur with LV hypertrophy (15).

**Attenuation of atrial–renal reflexes in CHF.** An increase in atrial pressure, as occurs with CHF, has been shown to initiate several reflexes that have a beneficial effect on renal function. An increase in left atrial pressure suppresses the release of the antidiuretic hormone arginine vasopressin, and leads to a water diuresis that is abolished by vagotomy, the so-called Henry-Gauer Reflex (16). Another normal response to an increase in left atrial pressure is a decrease in renal sympathetic tone (17). An increase in atrial pressure also has been shown to increase atrial natriuretic peptide (18). These atrial–renal reflexes, which normally enhance renal sodium excretion, are impaired during CHF because renal sodium and water retention occur despite elevated atrial pressures. Chronic CHF in the dog has been shown to be associated with a blunting of the atrial–renal sympathetic reflex (19). Although the elevated plasma vasopressin concentrations have been shown to be suppressed with an increase in atrial pressure in HF, the plasma levels of this antidiuretic hormone still remained increased and no diuresis occurred (20). Moreover, in contrast to normal subjects, plasma levels of atrial natriuretic hormone were found not to increase further during a saline load in patients with dilated cardiomyopathy and mild HF, and the natriuretic response was also blunted (21). There is also evidence that the attenuation of these reflexes on the low pressure side of the circulation is not only attributable to a blunting of the atrial–renal reflexes, but also may in part be caused by counteracting arterial baroreceptor–renal reflexes. There is evidence of autonomic dysfunction and blunted arterial baroreceptor sensitivity in CHF (22). This is associated with increased circulating catecholamines and renal sympathetic activity in CHF, and in fact plasma norepinephrine concentrations correlate with mortality (23). There is also evidence for parasympathetic withdrawal in CHF in addition to the increase in sympathetic drive (24).

**Activation of the renin-angiotensin-aldosterone system in CHF.** The renin-angiotensin-aldosterone system is known to be activated in patients with CHF, and in fact plasma renin activity also has been shown to correlate directly with mortality. Angiotensin II is known to cause myocardial remodeling (25), and aldosterone may increase myocardial fibrosis and necrosis in the heart (26). Moreover, angiotensin II is known to be a potent stimulator of the sympathetic nervous system (27). There is also experimental evidence for angiotensin generation in the central nervous system during cardiac failure, as evidenced by an increase in angiotensin concentration in the cerebrospinal fluid. Increased angiotensin and decreased nitric oxide in the brain have been implicated as mediators of the blunting of baroreceptor sensitivity in experimental CHF (28). The increase in renal sympathetic tone secondary to this baroreceptor perturbation would be expected to cause sodium retention by several mechanisms (Fig. 1). Angiotensin and renal nerve stimulation both activate receptors on the proximal tubule epithelium, which enhances sodium reabsorption (29,30). Furthermore, the resultant 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 (31). 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. Competitive inhibitors of the mineralocorticoid receptors in the distal nephron, i.e., spironolactone (32), can be used in HF to reverse the aldosterone-mediated sodium retention. These mineralocorticoid antagonists are the preferred diuretics in cirrhosis, and there are important similarities in the mechanisms of sodium retention in CHF and cirrhosis (33). There is, however, the danger of hyperkalemia in CHF patients treated with mineralocorticoid antagonists, particularly in the presence of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and/or

![Figure 1](Image) 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.
beta-blockers (34). The potassium-losing effect of loop and thiazide diuretics and a low potassium diet may, however, counterbalance the potassium-retaining effect of mineralocorticoid antagonists and thereby avoid the potential side effect of hyperkalemia. When mineralocorticoid antagonists are used to treat sodium retention in patients with CHF, the doses of spironolactone need in general to be higher than the 25 to 50 mg used for cardiac protection in the Randomized Aldactone Evaluation Study (35) to compete with the elevated endogenous concentrations of aldosterone. Because aldosterone has also been shown to cause renal fibrosis, mineralocorticoid antagonists may also exert a protective effect on the kidney in HF patients (36).

The juxtaglomerular apparatus of the kidney is a major mediator of the activation of the renin-angiotensin-aldosterone system. Specifically, renal beta-adrenergic stimulation (37) and decreased sodium chloride delivery to the macula densa (38), which are expected events with CHF, are known to stimulate the renin-angiotensin-aldosterone system. Moreover, with edema, the interstitial and venous pressure of the kidney may increase, perhaps in part because of the rigid renal capsule, and stimulate the renin-angiotensin-aldosterone system (31).

Thus, in CHF, activation of the renin-angiotensin-aldosterone system may cause progression of the 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, thereby perpetuating volume overload with the potential for cardiac dilation, LV hypertrophy, and blunting beneficial atrial-renal reflexes. Moreover, the resultant volume overload in HF patients is most frequently treated with loop diuretics, which block sodium chloride transport at the macula densa, with resultant further activation of the renin-angiotensin-aldosterone system (39).

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers have been shown to improve mortality in patients with symptomatic (3) and asymptomatic (2) HF. Nevertheless, the predominant vasoconstrictor effect of angiotensin on the efferent arteriole is important in maintaining glomerular hydrostatic pressure and thus the glomerular filtration rate. Therefore, inhibition of the angiotensin-convertase enzyme or angiotensin receptors in the patient with CHF may worsen renal function (40) and thereby perpetuate the sodium retention and volume overload, with the aforementioned deleterious consequences. The HF patients most likely susceptible to this adverse effect of angiotensin II inhibition are those who have already-elevated serum creatinine concentrations and are receiving diuretics.

There is another renal aspect of the treatment of CHF that is worthy of discussion. Cardiac afterload reduction with angiotensin inhibition or vasodilators may enhance cardiac index (41) and thereby improve renal function, including the capacity to maintain sodium and water balance. However, overly aggressive arterial vasodilation will cause relative arterial underfilling, and thus renal perfusion pressure, in spite of an increase in cardiac index. In this regard, a decrease in renal perfusion pressure has been shown to increase tubular sodium reabsorption (42) and thus potentially can worsen the deleterious effects of volume overload in the patient with CHF. Excessive arterial vasodilation to decrease cardiac afterload will further activate the renin-angiotensin-aldosterone and sympathetic systems.

The mechanisms that have been discussed thus far, whereby perturbations in kidney function may contribute to progression of cardiac disease by chronic volume overload and activation of the renin-angiotensin and sympathetic nervous systems are of a functional nature and are therefore potentially reversible. It must be acknowledged, however, that similar cardiac consequences of volume overload can occur as a consequence of intrinsic renal disease. For example, in CHF patients with diabetes or essential hypertension, renal microvascular disease may occur and lead to sodium and water retention and the cardiac consequences of volume overload.

**ROLE OF DIURETICS IN CHF: POSITIVE AND NEGATIVE ASPECTS**

The use of loop diuretics in CHF may worsen renal function (43). Because even mild renal dysfunction has been associated with increased cardiovascular mortality, the positive and negative aspects of the use of diuretics in patients with CHF must be considered. In symptomatic HF patients there is little question about the positive role of diuretics in treating congestion of the lung and pulmonary symptoms of dyspnea and shortness of breath. Moreover, with severe pulmonary edema, hypoxia, hypercapnia, and metabolic acidosis may occur and depress myocardial function (44). In this setting, treatment with diuretics may not only benefit the pulmonary symptoms, but by correcting these acid-base disorders, cardiac function may improve.

On the other hand, as noted above, the use of diuretics in some cardiac failure patients may lead to deterioration of renal function. Thus, the question emerges whether these patients with CHF should be maintained in a volume overload state to maximize their cardiac index on the Frank-Starling curve and preserve renal function. Support for such a conservative treatment approach is generally adopted in those CHF patients whose blood urea nitrogen and serum creatinine levels increase during diuretic treatment. However, as discussed previously, if diminished renal function with increased cardiac filling pressure and ventricular dilation because of chronic volume overload is not just a marker of poor prognosis but rather is also a contributor to progression of cardiac dysfunction, a therapeutic dilemma frequently emerges with respect to diuretic therapy. Fluid removal by ultrafiltration may be recommended in this setting, in which the use of loop diuretics is associated with deterioration of renal function (45). Although a descending arm of the Frank-Starling curve has not been identified,
some CHF patients with renal dysfunction, i.e., increased blood urea nitrogen and serum creatinine levels, actually improve their renal function after diuretic-induced weight loss. The mechanism for this improvement may relate to the reversal of one or more of the factors discussed earlier, whereby chronic volume overload may cause deterioration of cardiac function (Fig. 2).

Fluid removal by ultrafiltration in patients with severe CHF may have theoretical advantages over loop diuretics. First, relative or absolute diuretic resistance may occur with advanced cardiac failure (46), even when a combination of large doses of loop diuretics and a thiazide diuretic are used. Moreover, the use of large doses of these diuretics may have deleterious effects on cardiac function by their potassium- and magnesium-losing properties. Second, the fluid removed by ultrafiltration is isotonic with plasma, whereas the diuresis with loop diuretics is virtually always hypotonic to plasma. Therefore, for the same volume of fluid removal, ultrafiltration removes more sodium than diuretic therapy and also avoids electrolyte disturbances. Because sodium and its anion are the major determinants of ECF volume, ultrafiltration decreases ECF volume more than a comparable volume of diuretic-induced fluid loss. Moreover, as discussed earlier, loop diuretics block sodium chloride transport at the macula densa and thus activate the renin-angiotensin-aldosterone system (39) with its accompanying potential deleterious effects in the patients with CHF. However, because the role of fluid mobilization from the interstitium to vascular compartment is limited to 12 to 14 ml/min in HF (47), an over-aggressive rate of fluid removal by ultrafiltration may also activate the renin-angiotensin-aldosterone system. Nevertheless, for loop diuretics to be effective, they will always inhibit sodium chloride transport in the thick ascending limb of the loop of Henle including the macula densa, and thereby consistently stimulate the renin-angiotensin-aldosterone system. Stimulation of the renin-angiotensin-aldosterone system as a consequence of loop diuretic use has been shown to be a major factor in the occurrence of diuretic resistance (46). Recently, in a randomized study of a tachycardia-induced porcine model of HF, furosemide administration shortened the time to LV dysfunction and elevated serum aldosterone levels as compared with placebo independent of detectable differences in cardiac pre-load (48).

Despite the theoretical advantages of fluid removal by ultrafiltration over loop diuretics in the patient with advanced CHF and the reported beneficial effects in non-randomized studies of small numbers of patients (47), a prospective randomized study will be needed to establish an advantage of ultrafiltration over diuretic-induced therapy in CHF. Moreover, ultrafiltration is an invasive procedure and is more costly than diuretic treatment. Nevertheless, if ultrafiltration in selective patients is shown in future studies to decrease hospitalizations for HF (approximately one million/year in the U.S.), the treatment may be shown to be cost effective in some settings.

Recently, phase III studies with a vasopressin receptor antagonist in HF patients have shown weight loss associated with electrolyte-free water excretion without changes in blood pressure, renal function, or neurohumoral hormones (49). However, it must be remembered that with electrolyte-free water excretion after equilibration, only one-third of the volume loss will be from extracellular fluid, with the remaining loss from the intracellular component.

In addition to the antagonism of the V2 vasopressin antagonist on the renal collecting duct with the resultant water diuresis, there are theoretical reasons why antagonism of the V1a vasopressin receptor on cardiomyocytes and vascular smooth muscle could also be of therapeutic benefit in cardiac failure (Fig. 3).

Figure 4 shows how renal sodium retention can feed back and diminish plasma aldosterone and return cardiac index to near normal values. Thus, observing heart failure patients at only one snap shot in time, rather than observing the entire continuum can be misleading. Other circumstances where heart failure may be associated with renal dysfunction but a normal cardiac output include patients with diastolic dysfunction, impaired baroreceptor activity, and/or renal parenchymal disease (i.e., renal-cardiac syndrome).

**CHRONIC KIDNEY DISEASE AS A RISK FACTOR FOR CARDIOVASCULAR OUTCOMES**

Studies in high-risk cardiovascular populations and patients with cardiovascular disease have consistently shown that the level of kidney function is an independent risk factor for cardiovascular mortality (6,7). Chronic kidney disease has been defined as an estimated glomerular filtration rate of <60 ml/min/1.73 m². At this level of kidney function a number of cardiovascular risk factors may occur, including volume expansion secondary to sodium retention, hypertension, and insulin-resistance with impaired glucose tolerance. Chronic kidney...
disease has also been associated with increased oxidative stress, evidence of inflammation (e.g., increased c-reactive protein) (50,51), phosphate retention with medial vascular calcium (52), increased parathyroid hormone concentrations with myocardial calcification and dysfunction (53), and anemia and LV hypertrophy (54), all of which could increase cardiovascular disease (55) (Fig. 5). Increased plasma homocysteine, fibrinogen, and uric acid are other cardiovascular risk factors that occur with chronic kidney disease (56). Albuminuria has clearly been shown to be not only a risk factor for progression of chronic kidney disease but also a risk factor for cardiovascular mortality (57). Although some of these factors may only be markers of cardiovascular disease, it is clear that some are pathogenetic factors for cardiovascular outcomes. The Chronic Renal Insufficiency Cohort (CRIC) study should provide insight into the temporal relationship between these renal factors and the cardiovascular complications (58).

In a recent analysis of four community-based studies of 22,634 subjects without a history of cardiovascular disease, chronic kidney disease was shown to be a risk factor for the primary composite outcome of myocardial infarction, fatal coronary artery disease, stroke, and diabetes (7). However, in a sub-group analysis of the black population, chronic kidney disease was a greater risk factor for the primary composite cardiovascular end point than in the general population. The black population at baseline also had a history of more diabetes and hypertension (7).

In a recent study of elderly patients with HF and LV dysfunction, treatment with angiotensin converting enzyme inhibitors significantly decreased the risk of death independent of gender, age, race, or serum creatinine level (59). However, the inhibitors were underprescribed, and an elevation of serum creatinine level was the most significant predictor of failure to prescribe this proven effective treatment.

CHRONIC KIDNEY DISEASE AS A RISK FACTOR FOR OUTCOMES AFTER AN ACUTE MYOCARDIAL INFARCTION

There are several studies in which subjects with chronic kidney disease were found on follow-up to be associated with increased mortality after a myocardial infarction (60,61). This finding has been observed not only in elderly subjects after an acute myocardial infarction (62) but also in a more general population after a heart attack (63). As described above, there are several factors with chronic kidney disease that could be pathogenetic factors and/or markers of cardiovascular outcome after an acute myocardial infarction. In a recent study of 14,527 patients with acute myocardial infarction complicated by clinical or radiological...
signs of HF, LV dysfunction, or both, the risk of cardiovascular death increased with declining estimated glomerular filtration rate (GFR) beginning at a value <81 ml/min/1.73 m² (64). In an accompanying editorial, Hostetter (65) emphasizes the importance of calculating GFR, e.g., the Modification of Diet in Renal Disease (MDRD) formula (66) rather than using serum creatinine in such studies. This is because of the non-linear relationship between serum creatinine concentration and GFR, as well as the influence of age, gender, and race.

**SMALL INCREASES IN SERUM CREATININE AS A CARDIOVASCULAR RISK FACTOR FOR OUTCOMES AFTER CARDIOVASCULAR SURGERY**

Acute renal failure in patients undergoing cardiac surgery has been identified as the strongest risk factor for death, and the mortality may approach 80% (67). Recently, however, it has been reported that even minimal increases in serum creatinine (>0.5 mg/dl) within 48 h after cardiothoracic surgery in 3,381 patients with a baseline serum creatinine level <1.3 mg/dl was associated with increased 30-day mortality (hazard ratio, 7.09%) independent of the other variables, including the need for renal replacement therapy (5). This result is supportive of previous studies, which have shown that small increases in serum creatinine level after cardiac surgery are associated with increased non-renal complications and a poor prognosis (68,69). One explanation for this relationship is that a small increase in serum creatinine concentration after cardiothoracic surgery may be a sensitive marker of diffuse hypoperfusion throughout the body.

Even a small increase in serum creatinine concentration after cardiothoracic surgery may, however, be a contributing factor to increased complications and mortality. For example, as serum creatinine doubles, renal function decreases by 50% (e.g., an increase in serum creatinine from 0.8 to 1.6 mg/dl equates to a decrease in glomerular filtration rate from 100 to 50 ml/min) and the renal capacity to excrete administered fluid is impaired. With fluid overload and hypoxia, mechanical ventilation may be instituted. It is well established that the longer the period of ventilatory support, the higher the mortality from pulmonary infection, oxygen toxicity, barotrauma, and ultimately acute respiratory distress syndrome (70). Excessive fluid administration and more prolonged need for ventilatory support could be the reason why a >0.3 mg/dl decrease in serum creatinine concentration (i.e., 1.67 to 1.11 mg/dl; p < 0.001) within 48 h after cardiothoracic surgery was also shown to be a risk factor for 30-day mortality (5).

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