Renal dysfunction is highly prevalent in patients with heart failure. Furthermore, worsening renal function in patients with acute decompensated heart failure (ADHF), the so-called cardiorenal syndrome, impacts short and long-term morbidity and mortality. In recent years, more evidence has surfaced from clinical trials and heart failure registries that a complex cross-talk between the kidney and heart in patients with ADHF exists. Meanwhile, management of patients presenting with ADHF and concomitant renal dysfunction continues to be challenging. Therefore, understanding the interaction of the heart and kidneys is pivotal in tailoring therapy of these patients. We have extensively reviewed the pathophysiology of ADHF, the role of neurohoromones as well as other biomarkers and predictors of mortality in these patients based on the current evidence. Moreover, we have discussed the current and future pharmacologic and non-pharmacologic therapies for treatment of this deadly disease. The strength of the evidence is limited, however, due to a paucity of randomized controlled trials in this patient population. What is evident from current national statistics; however, are the poor results in treating the congestion of ADHF. In this regard, the role of secondary hyperaldosteronism is discussed in the diuretic section as well as diuretic resistance in ADHF. In conclusion, since renal function is the single most important prognostic factor in the outcome of patients with ADHF, a better understanding of the pathophysiology of the cardiorenal syndrome is needed to target therapy and ultimately improve the mortality of patients with ADHF.


Heart failure (HF) is a chronic and progressive disease that affects approximately six million Americans, with an incidence of 600,000 new cases each year (1). The interaction between heart and kidney disease has been an area of considerable interest in recent years. Renal impairment is a common and independent risk factor of morbidity and mortality (2,3) in this population, either in asymptomatic (4) or symptomatic (5) congestive heart failure (CHF) patients. Moreover, chronic kidney disease (CKD) plays a significant role in the progression of cardiovascular disease regardless of the status of the heart (6–8). The cross-talk between the kidneys and the heart is important to control BP, renal sodium and water excretion, arterial perfusion and oxygenation of tissues, and, most importantly, the extracellular fluid balance, including intravascular volume; therefore, when one organ becomes dysfunctional the other organ may be affected as well.

The “cardiorenal syndrome” terminology has been used more frequently in the last decade to define this interdependency of the kidney and the heart. In HF, it is the result of interactions between the heart and kidneys that increase circulating blood volume and symptoms of HF, and disease progression occurs. At its extreme, cardiorenal dysregulation leads to cardiorenal syndrome, in which therapy to relieve congestive symptoms of HF may be limited by further decline in renal function (9).

In this review, we explore the important aspects of the cardiorenal axis and define the role of kidney function and other risk factors in patients with acute decompensated heart failure (ADHF).

Epidemiology
Many landmark HF trials did not include patients with significant CKD; therefore, the majority of epidemiologic information of CKD in the HF population stems from large registries such as the Acute Decompensated Heart Failure National Registry (ADHERE) (10,11), Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) (12), and EuroHeart Failure (EURO HF) (13). The incidence of CKD, i.e., GFR (GFR) <60 ml/min (stage III), in HF patients comprises a wide range, from 20 to 67% (11–14), with higher incidence associated with elderly age, female gender, baseline CKD, Caucasian American race (12), diastolic heart failure (15), history of HF, diabetes, and systolic BP >160 mm/Hg.

The prevalence of diabetes, hypertension, and coronary artery disease (CAD), all risk factors for CKD and HF, increases with worsening of the kidney function (12,16). Worsening renal function has a significant impact on the length of hospital stay, higher intensive care unit admissions and mechanical ventilation intervention, mortality, and requirement for cardiopulmo-
nary resuscitation (12). In the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF), a randomized controlled trial of acute HF patients treated with intravenous milrinone, the incidence of death or readmission in 60 d was 35% (17). In another study of patients hospitalized for acute cardiac failure, a readmission rate of 20% and 50% at 30 d and 6 to 12 mo, respectively, is reported. The mortality in the same cohort was 10% and 20 to 40% at 30 d and 6 to 12 mo (16), respectively. Thus, a better understanding of the pathophysiology and optimal treatment of these patients with acute HF is required.

Currently, HF has affected 2.3% of the population, particularly the elderly (1), with an annual cost of more than 33 billion dollars (1). The majority of cost occurs during hospitalization. As the U.S. population ages and with the current epidemic of obesity, which leads to a surge in the incidence of diabetes and hypertension, the higher prevalence of HF seems inevitable, with a projected prevalence of 20% occurring in a couple of decades (17).

Pathophysiology of Cardiorenal Syndrome

The term cardiorenal syndrome has repeatedly been used as an umbrella terminology for worse outcome when these two organs fail simultaneously. However, the pathophysiology of kidney disease in HF is quite different from the pathophysiology of cardiovascular complications in the setting of CKD (6). When renoparenchymal disease leads to cardiovascular complications, it is reasonable to name the latter condition as “renocardiac syndrome” (18). This review exclusively focuses on the renal insufficiency that occurs secondary to HF.

Cardio-Renal Axis

Normally, the cross-talk between the heart and the kidneys occurs through atrial-renal reflexes (6), which contribute to maintaining the total body volume in the normal range. In a nonfailing heart, any increase in atrial pressure diminishes the arginine vasopressin release (AVP) (19) through the Henry-Gauer Reflex, decreases renal sympathetic tone (20), and increases the atrial natriuretic peptide (21), all of which increase the urinary sodium and water excretion rate. In HF, however, there is blunting of these reflexes in the low-pressure circulation, probably secondary to being overridden by reflexes initiated in the high-pressure arterial circulation.

Neurohormones in Heart Failure

The renin-angiotensin-aldosterone system has an important role in the initiation and maintenance of edema in HF (6,18,22,23). Increased renin secretion occurs early in biventricular failure (24), which leads to stimulation of angiotensin II (Ang II). Ang II has many physiologic effects, which include stimulation of central neural centers associated with increased thirst and heightened activity of ganglionic nerves via its effects on the autonomic nervous system (25). Ang II also serves as a systemic vasoconstrictor to compensate for the initial decrease in stroke volume associated with ventricular failure. This is, however, only one of a myriad of factors that increase peripheral vasoconstriction to restore arterial pressure and improve cardiac output (24,25). Ang II is also known to be a potent stimulator of the sympathetic nervous system (6), which will increase the systemic vascular resistance.

Ang II increases aldosterone synthesis (26), which increases renal sodium reabsorption and causes sodium retention. In normal subjects an “escape” from renal salt-retaining effects of aldosterone occurs usually after a 3-d period (24,25), thus avoiding edema formation. This aldosterone escape phenomenon, however, does not occur in HF patients and the continued sodium retention contributes to the pulmonary congestion and edema (6,24,25). Aldosterone also increases the myocardial fibrosis of the failing human heart (26). Moreover, patients with biventricular failure may also have poor hepatic perfusion and decreased clearance of aldosterone, thereby contributing to an elevation in the plasma aldosterone concentration (24).

Catecholamines have a vital role in HF. Braunwald et al. demonstrated in HF that there is a decrease in cardiac norepinephrine (NE) levels, while the plasma NE is elevated (27). This decrease in cardiac NE is the result of maximal turnover of myocardial NE. Thus, the failing heart cannot respond adequately to sympathetic stimulation since the NE turnover rate has already been maximized. It is well known that elevated plasma NE levels in patients with HF correlate with increased mortality (28,29). Meanwhile, renal effects occur secondary to activation of the sympathetic nervous system (SNS). Stimulation of α-receptors on the proximal tubule of the nephron enhances the reabsorption of sodium, while β-receptors in the juxtaglomerular apparatus stimulate the renin-angiotensin-aldosterone system (RAAS) (6). Moreover, in HF, postglomerular capillary pressure falls and oncotic pressure rises, further enhancing proximal tubular reabsorption (6).

Atrial natriuretic peptide (ANP) is stored in the perinuclear granulocytes in cardiac atria and released in response to atrial stretch mechanisms (30). ANP increases GFR, sodium and water excretion; causes vasodilatation; and decreases RAAS, vasopressin, and SNS. The increase in GFR occurs secondary to dilation of the afferent arteriole and constriction of the efferent arteriole. Natriuretic peptides also directly decrease tubular sodium reabsorption (6,19,20). These effects of natriuretic peptides are attenuated in advanced HF, due to renal vasoconstriction and reduced sodium delivery to the distal nephron where natriuretic peptides inhibit sodium reabsorption (6,29). The other possibility of diminished lack of natriuretic effect of BNP in HF patients despite elevated levels is downregulation of the BNP receptors (25).

Arginine vasopressin (AVP), the antiuretic hormone, is secreted from the posterior pituitary gland and is released secondary to arterial underfilling and increased osmolality. In HF there is the nonosmotic release of this peptide (31). AVP stimulates the V1a receptors of the vasculature and increases systemic vascular resistance, while stimulation of the V2 receptors in the principal cells of the collecting duct increases water reabsorption and leads to hyponatremia. AVP also enhances urea transport in collecting ducts of the nephron, thereby increasing the serum blood urea nitrogen (BUN).

The activation of the neurohormonal system leads to sodium and water retention, pulmonary congestion, and hyponatremia,
which occurs both in low-output and high-output cardiac failure (23,32,33) (Figure 1). The arterial underfilling occurs secondary to a decrease in cardiac output in low-output HF and arterial vasodilatation in high-output HF, both of which decrease the inhibitory effect of the arterial stretch baroreceptors on the SNS and the RAAS. Decreased baroreceptor sensitivity also contributes to stimulation of RAAS and SNS. Thus, a vicious cycle of worsening HF and edema formation occurs (Figure 2).

Congestion

Registry data have shown that it is the pulmonary congestion that brings the patients to the hospital (10–13). In the ADHERE registry, 50% of patients who were admitted to the hospital had a systolic BP of 140 mm/Hg or higher and only 2% had a systolic BP of <90 mm/Hg (10). The increase in BP may relate to pulmonary congestion with exercise-related hypoxia a known stimulator of the SNS. This increase in BP can facilitate redistribution of the blood from the intravascular to the interstitial compartment. This may enhance the pulmonary congestion irrespective of total intravascular volume.

Sodium and water retention also increases preload with cardiac dilation and ultimately causes cardiac remodeling. This vicious cycle subsequently leads to functional mitral regurgitation, pulmonary hypertension, and increased ventricular wall stress (6). Moreover, since most of the volume expansion is on the venous side of the circulation, leftward deviation of the interventricular septum occurs and impairs diastolic function (6). Volume overload and elevated cardiac preload ultimately lead to high transmural myocardial pressure, increased left ventricular (LV) mass index (6) and LV hypertrophy (LVH). LVH is associated with a diminished ratio of capillaries to cardiac myocyte that causes myocardial ischemia, even in the absence of CAD (6).

Renal Dysfunction in HF

A common misconception is that worsening renal function in ADHF is either due to decreased intravascular volume and/or low cardiac output. Gottlieb et al. have shown that 47% of patients admitted for ADHF had worsening renal function during the first 3 d of hospitalization, when patients were still hypervolemic (34). Clearly overdiuresis and lowering filling pressure can potentially worsen renal function, but it is not the case in almost half of ADHF admissions.

In ADHF, release of vasoconstricting and sodium-retaining neurohormones such as Ang II, NE, endothelin, adenosine, and arginine vasopressin occurs. However, vasodilatory and natriuretic hormones such as natriuretic peptides, prostaglandins, bradykinin, and nitric oxide also occur in HF and counterbalance these effects (35). The imbalance between the vasoconstriction/sodium retention and vasodilatation/natriuresis in favor of the former is pivotal in worsening renal function and sodium retention in these HF patients.

Increased cardiac preload is associated with increased renal venous pressure. Renal perfusion pressure is equal to mean arterial pressure minus left atrial pressure (LAP), as an index of renal venous pressure. An elevated central venous pressure has been shown to decrease GFR and cause sodium and water retention (36,37). An increase in renal venous pressure can also stimulate the RAAS (37). Therefore, elevated right and left ventricular end-diastolic pressure and venous pressure not only impair forward flow, i.e., cardiac output, but can also contribute to renal dysfunction by increasing renal venous pressure.

Elevated adenosine in HF could decrease GFR by vasodilatation of postglomerular capillaries, vasoconstriction of preglomerular afferent arterioles, or both. Another important action of adenosine is as a mediator of activated tubulo-glomerular feedback (TGF), which can decrease GFR (38).

Renal dysfunction in patients with ADHF can be caused or further complicated by contrast agents, nonsteroidal anti-inflammatory agents, and other nephrotoxic drugs.
Risk Stratification and Predictors of Mortality in ADHF

The number of hospital discharges for HF has increased by 174% between 1979 until 2004 (1). The incidence of mortality and readmission in patients with ADHF is unacceptably high, in the range of 20% to 50% (16,39). The in-hospital mortality rate for ADHF in registries and clinical trials is very similar. It is 3.2% and 3.8% in OPTIMIZE-HF and ADHERE registries (12,40), respectively, and 3.8% and 4.8% in OPTIME-HF and Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) clinical trials (17,41), respectively. Therefore, risk stratification of these patients for intensification of diuretic therapy and/or device therapy is based on the patient’s baseline risk of mortality. To assess these risk factors, different groups have analyzed the data from the registries, such as ADHERE and OPTIMIZE-HF, and clinical trials such as Candesartan in Heart Failure Assessment of Reduction of Mortality and Morbidity (CHARM) (42). One of the advantages of the CHARM investigator outcome study is that it examined the HF patients with preserved ejection fraction (HFPEF). In the ADHERE registry, 50% of the patients presented with HFPEF (11,43).

Laboratory Parameters

I. Blood Urea Nitrogen (BUN)

Fonarow et al. analyzed data in the ADHERE registry, using the classification and regression tree (CART) analysis approach. Admission BUN of more than 43 mg/dl was found to be the best identifier of in-hospital mortality in patients with ADHF (44). Lower systolic BP and higher serum creatinine were the second and third best identifiers, respectively.

This BUN effect was confirmed by another retrospective analysis of OPTIME-CHF by Klein et al. (45). In their analysis, they concluded that not only the admission BUN, but the change in BUN during hospitalization, had the most important impact on the outcome in 60 d. In this study, BUN was analyzed by quartiles. Interestingly, the highest BUN quartile was associated with lowest BP, lowest plasma sodium concentration, highest jugular venous pressure (JVP) (45), and, therefore, worse outcome (46,47). As previously noted, the low cardiac output leads to significant neurohumoral activation, including the nonosmotic release of AVP (31). This stimulation of AVP release results in enhanced reabsorption of urea through urea transporters in the collecting duct (48). This may be the explanation why BUN was found to correlate with 60-d mortality more than either serum creatinine or eGFR. Moreover, in ADHF increased plasma AVP is associated with activation of RAAS and SNS, known predictors of mortality (25). Thus, BUN depends on both cardiac and kidney function, as it takes into account cardiac output and is a marker of neurohormones (48). As noted, renal venous pressure also is a major determinant of renal function in worsening HF.

II. B Type Natriuretic Peptide (BNP)

There are two major natriuretic peptides produced by the heart: ANP in the atria and BNP in the ventricles (49). In HF, congestion causes cardiac chamber stretch and this leads to release of these hormones. Harrison et al. evaluated the prognostic importance of elevated levels of BNP in patients who presented to the emergency room in different BNP tertiles (50). Patients with HF who presented with BNP level of >480 pg/ml had a 51% chance of death, hospital readmission, or emergency room visit in 6 mo, as opposed to 2.5% in HF patients who had a BNP level of <230 pg/ml.

III. Troponin

Cardiac-specific troponins I and T are highly sensitive and specific markers of myocardial injury. Approximately 40% of patients who are admitted to the hospital with ADHF have plasma elevations in troponin that are not associated with any EKG changes or findings of acute ischemia (51). In the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study (52) of more than 4000 patients in Canada, the investigators found cardiac troponin I elevation (>0.5 μg/L) was a strong and independent predictor of all-cause mortality with a hazard ratio (HR) of 1.49 (95% CI 1.25 to 1.77, P < 0.001). This finding was consistent across subgroups and was observed in patients with no other evidence of acute ischemia on presentation.

In a recently published analysis of the ADHERE (53) registry, there was a strong association between elevated troponin, either I or T subtypes, and mortality. Overall, 6.2% of patients had a positive result for troponin (troponin I >1 μg/L or troponin T >0.1 μg/L). Patients with positive troponin had lower systolic BP on admission, a lower ejection fraction, and higher in-hospital mortality (8.0% versus 2.7%, P < 0.001) compared with those with negative troponin. The adjusted odds ratio for death in the group of patients with a positive troponin was 2.55 (95% CI 2.24 to 2.89, P < 0.001).

IV. Hyponatremia

Hyponatremia is common in patients with ADHF. Lee et al. (54) demonstrated that hyponatremia has associated with higher mortality in chronic HF patients. This grave outcome occurs in the ADHF patients as well. In the analysis of OPTIMIZE-HF registry (47), 19.7% of patients were admitted with hyponatremia (Na <135 mMol/L). Interestingly, the incidence of hyponatremia is comparable in registries as in clinical trials, including OPTIME-CHF (55) (27%) and ESCAPE (56) (24%). Not only is a lower serum sodium concentration associated with higher mortality (47,55,56) during hospitalization and postdischarge, but it also correlates with a higher risk of readmission within 6 mo for ADHF when comparing hyponatremia versus normonatremia (62% versus 43%; HR = 1.52, P = 0.03) (56).

Plasma vasopressin is increased in HF and the level is proportional to severity of HF (6,25). Vasopressin stimulation of the V1 and V2 receptors can potentially worsen the signs, symptoms, and LV function of patients with acute HF (Figure 3). Stimulation of the V2 receptors on the collecting duct principal cells by vasopressin causes water retention and hyponatremia. Blocking the V2 receptor vasopressin corrects hyponatremia in HF (57–60) and improves dyspnea. However, there are no data that correction of hyponatremia leads to better survival outcome in patients with ADHF (59,60).
V. Anemia

Anemia is a common finding in patients with HF, regardless of the presence of kidney parenchymal disease. The mechanism of anemia in CHF is almost certainly multifactorial. Congestion with renal sodium and water retention will lead to hemodilution. When worsening renal function occurs in HF patients, relative erythropoietin deficiency may ensue (61). Inflammation and increased cytokine production occur with HF and can suppress erythropoiesis by the bone marrow (62). Nutritional and vitamin deficiency is also common in patients with HF and may contribute to anemia.

An analysis of the database of the Study of LV Dysfunction (SOLVD) by Al-Ahmad et al. showed that for every decrease in hematocrit of 1% the mortality rate increases by 2.7% (63). Moreover, a number of small studies in chronic heart failure patients have shown significant improvement in outcomes by increasing hemoglobin level up to 12 to 13 g/dl (64). On the other hand, the Correction of Hemoglobin and Outcomes In Renal Insufficiency (CHOIR) study (65) in CKD patients with anemia receiving alfa epoetin led to increased hospital admission due to CHF exacerbation. Furthermore, a statistically significant increased rate of death and cardiovascular events was observed.

Currently, Reduction of Events With Darbepoetin Alfa in Heart Failure (RED-HF) trial (66) is enrolling up to 3600 patients in a double-blind, randomized controlled trial. The primary endpoint of the study is a composite of time to death from any cause or first hospital admission for worsening heart failure. The result of this study should have an important impact in regard to the target hemoglobin in HF.

Clinical Parameters

I. Renal Insufficiency

A significant number of patients with ADHF have baseline renal insufficiency. Yet perhaps more important is the change of renal function during hospitalization. Gottlieb et al. have shown that even a small increase in serum creatinine (Cr), e.g., 0.1 mg/dl (34) will worsen the outcome of the patients. It is also noteworthy that a significant rise in serum Cr generally may occur in the first 3 d of the admission to the hospital (34). The mortality rate in ADHERE registry is 4% for all the patients; however, the mortality of patients with significant renal insufficiency, i.e., Cr >3 mg/dl, is 9.4% (67), and the length of hospital stay is also lengthened as compared with those who do not have renal insufficiency (67).

In another study of 1681 patients admitted for ADHF, Krumholz et al. found worsening renal function during hospitalization in 28% of patients (68). In-hospital mortality was more than double in those with versus without worsening renal function (7% versus 3%). This significant difference remained at 30 d (10% versus 6%) and 6 mo (25% versus 19%) (68).

The CHARM investigators also studied predictors of outcome in all three component trials in 2680 patients for an average of 34 mo. They found that every 10 ml/min decrease in eGFR increased the adjusted HR of cardiovascular death or readmission to the hospital by 10% (1.10, CI 1.07 to 1.13, P < 0.001) (42). Therefore, even small changes in Cr have an important impact on in-patient mortality as well as postdischarge mortality (34,42).

II. Blood Pressure

Unlike the clinical trials, in which most of the patients have low or low-normal BP, both registries of ADHERE and OPTIMIZE-HF demonstrated that in ADHF patients, the mean arterial BP is frequently >140 mm/Hg (11,43). Whether this increased BP is secondary to acute SNS stimulation related to acute dyspnea, pulmonary edema, or hypoxia is not known. Patients with ADHF are, however, clearly stressed at hospitalization.

Gheorghiade et al. (69) in an examination of OPTIMIZE-HF registry cohort, showed that systolic hypertension is not only common in patients hospitalized with acute HF, but it correlated inversely with mortality in hospital and for 60 to 90 d after discharge, regardless of admission LV systolic function. For admission systolic BP readings <160 mmHg, the HR for inhospital death increased 21% (95% CI 1.17 to 1.25) for every 10-mm-Hg fall; the risk didn’t vary for systolic BP values >160 mmHg. Also, for every 10-mm-Hg decrease in systolic BP, the postdischarge mortality HR rose by 18% (95% CI 1.10 to 1.26) and the HR for the composite of mortality or rehospitalization rose 5% (95% CI 1.03 to 1.07). Despite the fact that higher systolic BP was associated with lower mortality, it did not change the readmission rate in any of the BP quartiles. In one study of 1004 patients, however, Forman et al. found worse outcome in patients admitted with ADHF whose systolic BP was higher than 160 mm/Hg (70).

III. QRS Duration

Wang et al. in a retrospective analysis of Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial found that 44% of patients upon entry to the trial had baseline QRS duration of more than 120
msec. The QRS duration did not change during hospitalization or postdischarge; however, QRS prolongation was associated with a nonsignificant 30% increase in adjusted risk of mortality and a significant 41.6% increase in adjusted risk of cardiovascular death or hospitalization over 3 mo (71). These findings are striking in an era of device therapy for HF, and it underscores the importance of appropriate usage of devices such as cardiac resynchronization therapy for this patient population.

IV. Hypothermia

Ang II regulates body temperature through AT1 receptors (72). Ang II reduces core body temperature by decreasing metabolic rate as well as increasing radiated heat (34). These effects could be blocked by losartan in rats (34). In a study of National Heart Care (NHC) project, a large national quality-of-care initiative in hospitalized patients with HF, Brahmajee et al. found a strong correlation between a body temperature <36°C and increased mortality both in-hospital and at 1-yr mortality (73).

In an analysis of patients in Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) trial (74), an oral body temperature of less than 35.8°C was associated with an increased incidence of mortality at 60 d, 9.4% versus 5.9%. Hypothermic patients had a 3.9 times higher chance of death in 60 d than nonhypothermic patients (95% CI 1.002 to 15.16, \( P = 0.05 \)) after adjustment for multiple confounders.

V. Coronary Artery Disease (CAD)

Recent analysis of registries and clinical trials demonstrate that a majority of patients with HF carry a diagnosis of CAD. In the Carvedilol Hibernation Reversible Ischemia Trial; Marker of Success (CHRISTMAS), Cleland et al. demonstrated that 60% of patients with ADHF have hibernating myocardium, which is specifically susceptible to ischemia (75). This is relevant in relation to the increase in cardiac troponin I and T as markers of myocardial damage in ADHF patients admitted to the hospital (50–53). Thus, in ADHF, elevated LV end-diastolic pressure, CAD, and activation of neurohormones predispose to myocardial injury.

A recent analysis of OPTIMIZE-HF demonstrated a 14% higher in-hospital mortality in patients with CAD as compared with patients who do not have CAD (3.7% versus 2.9%, HR 1.29, 95% CI 1.14 to 1.46, \( P < 0.0001 \)) (76). Postdischarge mortality at 60 to 90 d was also increased by 37% (9.2% versus 6.9%, HR 1.46, 95% CI 1.14 to 1.85, \( P = 0.002 \)) in the presence of CAD (76). These effects were independent of LV function. Lastly, CAD patients who had coronary revascularization had the same mortality as ADHF patients without CAD. Thus, it is important to appreciate the importance of CAD in patients who are admitted for ADHF as it relates to potential coronary intervention.

Management of HF with Impaired Kidney Function

The clinical challenges in management of ADHF are several, including avoiding further renal impairment and hypotension, achieving electrolyte balance, and management of diuretic resistance. Therefore, the goal of therapy is to stabilize hemodynamics without further myocyte damage, arrhythmias, worsening renal function, and hypotension. Angiotensin-converting enzyme (ACE) inhibitors/angiotensin-receptor blockers (ARBs), beta blockers, and non-natriuretic doses of spironolactone, i.e., 25 mg/d, have decreased mortality in chronic HF patients, but the mortality of ADHF remains high.

Current therapy includes diuretics, natriuretic hormones, aquaretics (arginine vasopressin antagonists), vasodilators, and inotropes. There are also investigational therapies such as adenosine A1 receptor antagonists, ultrafiltration, and calcium sensitzers (levosimendan).

1. Diuretics: Advantages and Disadvantages

Loop diuretics are the mainstay pharmacologic treatment for the management of ADHF patients with volume overload (88%) (11). Intravenous diuretics most commonly used in the management of ADHF are listed in Table 1. They are recommended as the first line of therapy by Heart Failure Society of America updated guidelines (77), because they rapidly lower the ventricular filling pressure and reduce pulmonary congestion. When HF patients are admitted with pulmonary edema and/or systemic congestion, there is little doubt about the advantage of using loop diuretics. This leads to improvement of symptoms and may even improve kidney function by decreasing renal venous pressure (36,37).

Adverse events, however, may occur with the use of loop diuretics, such as electrolyte abnormalities, hypotension, and worsening renal function (77–79) (Figure 4).

- Loop diuretics can cause significant electrolyte abnormality, which might lead to significant arrhythmias (decrease in potassium, magnesium, calcium, and sodium) (78).

- In general, judicious use of loop diuretics does not decrease BP, but in the setting of ADHF, especially if vasodilator therapy is concomitantly used, hypotension is a common side effect. In patients with systolic dysfunction and decreased cardiac preload, aggressive diuresis may cause hypotension.

- Inhibition of Na-K-2Cl channel by loop diuretics is associated with macula densa inhibition and stimulation of the RAAS system.

- Renal function may decrease by use of loop diuretics secondary to activation of neurohormones and diminished renal perfusion. This leads to an increase in BUN and Cr. On the other hand, an increase in diuresis not only improves pulmonary congestion but can also decrease ventricular cardiac dilation, a major risk factor for mortality in HF. Improved myocardial function may occur with diuresis secondary to diminished ventricular wall stress, decreased endomyocardial ischemia, and reversal of functional mitral insufficiency (Figure 5).

Diuretic resistance. Proposed mechanism for diuretic resistance includes decreased GFR (78), increased renal nerve activity (79), increased activation of RAAS (79), and hypertrophy of distal tubule epithelial cells (35,78). This can occur even with dietary sodium restriction, which is very important in treating ADHF. Given the potential reduced intestinal absorption of diuretics and altered pharmacokinetics and pharmacodynamics of diuretics, intravenous administration of this class is generally indicated. The steep dose-response curve of these
agents mandates a rapid titration of the dose by doubling the dose until appropriate response is achieved. There are strategies to overcome diuretic resistance. One approach is to use the continuous intravenous loop diuretic administration (Table 1). Several small studies have shown decreased length of stay and lower cardiac and all-cause mortality with continuous loop diuretic therapy (35). Prospective, adequately powered, randomized trials, however, are needed. Another approach to overcome diuretic resistance is administration of a second diuretic agent, which blocks the distal tubule to provide significant augmentation of the loop diuretic effects. Intravenous chlorothiazide (500 to 1000 mg) half an hour before administering loop diuretic is an effective strategy to increase urine output. Metolazone (2.5 to 10 mg) orally can also be administered. Yet, the long half-life of 5 to 7 d of metolazone may be problematic. Therefore, careful monitoring of the electrolytes and hemodynamics becomes more important in patients who receive metolazone. Major side effects of hypokalemia and hypomagnesemia must be avoided.

There are no randomized controlled trials comparing one loop diuretic to the other in ADHF. In vitro study in an animal model suggested that torsemide inhibits aldosterone secretion from adrenal cells (80). In diuretic-resistant patients, rotating the different loop diuretic (e.g., changing from furosemide to torsemide) has been reported to increase urine output (81). These observations, however, need to be evaluated in prospective randomized studies.

**Mineralocorticoid antagonists.** Low- and high-output HF are both hyperaldosteronism state. Thus, it may be necessary to use natriuretic doses of mineralocorticoid antagonist (>25 mg/d of spironolactone) with concomitant use of loop diuretics. This may prevent or attenuate diuretic resistance and allow better control of renal sodium and water retention. Pilot studies need to examine whether hyperkalemia can be avoided by a low-potassium diet and potassium-losing doses of loop diuretics in spironolactone-treated patients with ADHF. Two large, double-blind, randomized controlled trials (82,83) demonstrated significant reduction in mortality of patients with chronic CHF and HF due to postmyocardial infarction with mineralocorticoid antagonists. Neither one of these trials, however, has used natriuretic doses of either spironolactone or aldactone.

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**Table 1. Pharmacologic agents in the management of acute decompensated heart failure**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dose</th>
<th>Dose Range</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
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</tr>
<tr>
<td>Furosemide</td>
<td>20 to 80 mg IV bolus</td>
<td>20 to 400 mg boluses may repeat q6 to 8H</td>
<td>Infusion is recommended at 5 to 40 mg/h. If &gt;240 mg/h, risk of ototoxicity increases.</td>
</tr>
<tr>
<td>Torsemide</td>
<td>10 to 40 mg bolus</td>
<td>20 to 200 mg bolus</td>
<td>Continuous infusion: 5 to 20 mg/h</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>0.5 to 2 mg bolus</td>
<td>0.5 to 4 mg bolus</td>
<td>Continuous infusion: 0.1 to 0.5 mg/h</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.3 to 0.5 µg/kg/min</td>
<td>0.3 to 5 µg/kg/min</td>
<td>Infusion rates of &gt;10 µg/kg/min may cause cyanide toxicity. Also, caution in active myocardial ischemia.</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>10 to 20 µg/min</td>
<td>20 to 400 µg/min</td>
<td>Severe headache, hypotension, closed-angle glaucoma</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>No bolus</td>
<td>0.005 to 0.03 µg/kg/min</td>
<td>Titration: increased infusion rate by 0.005 µg/kg/min (no more than every 3 h, up to a maximum of 0.03 µg/kg/min).</td>
</tr>
<tr>
<td><strong>Vasodilators</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.3 to 0.5 µg/kg/min</td>
<td>0.3 to 5 µg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>10 to 20 µg/min</td>
<td>20 to 400 µg/min</td>
<td></td>
</tr>
<tr>
<td>Nesiritide</td>
<td>No bolus</td>
<td>0.005 to 0.03 µg/kg/min</td>
<td></td>
</tr>
<tr>
<td><strong>Inotropes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>2 to 5 µg/kg/min</td>
<td>2 to 20 µg/kg/min</td>
<td>May increase mortality. Caution for arrhythmia.</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>1 to 2 µg/kg/min</td>
<td>1 to 20 µg/kg/min</td>
<td>May increase mortality. Caution for arrhythmia.</td>
</tr>
<tr>
<td>Milrinone</td>
<td>50 µg/kg IV loading dose over 10 min; then 0.25 to 1.0 µg/kg/min infusion</td>
<td>0.10 to 0.75 µg/kg/min</td>
<td>May increase mortality. Caution for arrhythmia.</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levosimendan</td>
<td>0.05 to 0.2 µg/kg/min bolus over 10 min followed by infusion</td>
<td>0.5 to 2.0 µg/kg/min</td>
<td>May increase mortality. Not approved in the United States. Caution for hepatic impairment and left-ventricular outflow obstruction.</td>
</tr>
</tbody>
</table>
eplerenone. In an observational study, an increased incidence of hyperkalemia has been reported (84) since the publication of Randomized Aldactone Evaluation Study (RALES). A recent subanalysis of Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), however, demonstrated that use of eplerenone within the dose range of 25 to 50 mg/d in postmyocardial patients with HF and/or LV ejection fraction (LVEF <40%), who are otherwise treated with standard therapy, did not significantly increase the risk of hyperkalemia (85). Currently, there are no clinical trials with mineralocorticoid antagonists in ADHF. As mentioned before, sodium and water retention is a main factor in the pathophysiology and symptomatology of ADHF. The onset of action for spironolactone is slower than loop diuretics and the peak effect of spironolactone is 48 h. Therefore, with acute pulmonary edema, loop diuretics are the diuretic of choice. The role of mineralocorticoid antagonist in natriuretic doses is, however, in need of evaluation in patients with diuretic resistance or secondary hyperaldosteronism due to HF.

2. Natriuretic Hormones

Nesiritide, the synthetic BNP, has been rigorously used and studied in ADHF patients during the last decade. Nesiritide exerts its effects by activation of guanylyl cyclase-linked natriuretic peptide receptors A and B that ultimately cause cyclic guanosine monophosphate (cGMP)-mediated vasodilation of arterial and venous systems. Therefore, it reduces the cardiac filling pressure and improves dyspnea in patients with ADHF (86). This was shown in the Vasodilatation in the Management of Acute CHF study (VMAC), the only placebo-controlled study of nesiritide. Nesiritide reduces pulmonary capillary wedge pressure (PCWP) in 15 min, a statistically significant effect compared with placebo. However, this effect of nesiritide did not reach statistical significance when it was compared with nitroglycerin (NTG) (86).

There are, however, safety concerns for the use of nesiritide related to potential worsening of renal function (86). Sackner-Bernstein et al. in a meta-analysis of randomized, double-blind, parallel-group controlled trials with nesiritide in patients with ADHF found a significant increased risk of worsening renal function (87). However, all these studies were performed with a bolus of 2 μg/Kg followed by 0.01 μg/Kg/min infusion. In a retrospective case-control study, the safety of nonhypotensive doses of nesiritide (0.0025 or 0.005 μg/Kg/min), as compared with the larger recommended bolus and infusion, was tolerated well and demonstrated improvement in renal function (88).

As a potent vasodilator, nesiritide administration may be associated with relatively prolonged hypotension (2 h) despite the relatively short half-life of the drug itself (18 min). This hypotension is usually aggravated if the patient is volume depleted or uses high doses of loop diuretics. The physiologic response to hypotension is activation of the RAAS and SNS. Therefore, avoiding bolus dosing and using lower doses of nesiritide, i.e., 0.005 μg/Kg/min may avoid hypotensive episodes (Table 1). It is also reasonable to hold diuretics, at least for the first 24 h, so as to avoid further activation of the RAAS and SNS. Unfortunately, there is a paucity of large prospective clinical trials with lower doses of nesiritide.

3. Vasodilator

The parenteral use of NTG addresses the hemodynamic abnormalities in ADHF by reducing PCWP, right atrial (RA) pressure, and systemic and pulmonary vascular resistance, all of which can lead to decreasing congestion and increasing cardiac index (88). There have been reports that vasodilators may decrease BNP (89); however, there is also the potential of increasing plasma renin level (89). The effect of NTG on coronary blood flow has not been investigated in ADHF but is known to increase coronary flow in other scenarios. In patients

**Figure 4.** The mechanism of electrolyte abnormalities by loop diuretics.

**Figure 5.** Mechanism by which negative sodium and water balance may improve myocardial and renal function in CHF. [Reprinted from *J Am Coll Cardiol*, vol. 47, Schrier RW, Role of diminished renal function in cardiovascular mortality: Marker or pathogenetic factor? pp. 1–8, copyright 2006 (ref. 6), with permission from Elsevier.]
with CAD who present with ADHF, “coronary steal” may occur with NTG (89).

Nitroprusside is a very potent vasodilator with rapid onset and off-set action. It also alters the hemodynamic parameters in favor of reducing pulmonary congestion and increasing forward flow, as does NTG. A very common side effect of nitroprusside is hypotension, which may lead to worsening renal function and sometimes coronary ischemia. Another uncommon but potentially fatal complication, if left untreated, is accumulation of thiocyanate (89), especially in patients with renal failure.

Blockade of RAAS by starting low-dose ACE inhibitors or ARBs and up titration of the dose is an alternative approach in vasodilatation.

4. Inotropes
Short-term inotropic infusion, although frequently used to improve hemodynamics and symptoms in ADHF, remains controversial. When patients present with profound circulatory collapse, inotropes may be absolutely required. For patients with ADHF who have evidence of end-organ hypoperfusion or diuretic resistance, but no frank hypotension, the use of inotropic agents is not well supported.

Dobutamine is a synthetic catecholamine with mainly β1-receptor agonist and some β2-receptor activity, characteristics that make it an inotropic vasodilator. Use of milrinone, a phosphodiesterase III inhibitor, results in elevated levels of cyclic adenosine monophosphate in the myocardium and smooth muscle. This leads to increased cardiac contractility and vasodilation. Milrinone works via a different cellular signaling pathway than dobutamine; it therefore can be used simultaneously with catecholaminergic agonists or antagonists.

The use of dobutamine for inotropic support in ADHF has yielded mixed results in studies. An infusion of dobutamine for 3 to 5 d in patients with ADHF has been shown to improve symptoms for up to 30 d (90,91). However, intermittent dobutamine therapy in ambulatory patients with severe chronic heart failure showed a nonsignificant trend toward worse outcomes (92). The largest registry of patients with ADHF to date demonstrated a higher mortality with intravenous inotrope therapy as compared with NTG or nesiritide therapy (92). The use of digoxin has been shown to reduce rates of hospital admission among patients with chronic heart failure without a significant effect on mortality (93). The use of digoxin in ADHF has not been defined except for small studies examining the agent’s hemodynamic effects. Long-term digoxin therapy should not be stopped during ADHF, because this may worsen cardiac function in the short term.

OPTIME-CHF enrolled 951 patients who were admitted with hemodynamically stable exacerbations of systolic heart failure (16). Patients with evidence of frank cardiogenic shock were excluded. Within the first 48 h after admission, patients were randomly assigned to receive either a 48- to 72-h infusion of milrinone (initially 0.5 µg/kg/min) or placebo. No statistical difference was found between the two arms at 60 d for the primary endpoint of total days in hospital. In addition, mortality did not differ significantly between the two groups, although it tended to be higher in the milrinone group than in the placebo group (in-hospital mortality 3.8% versus 2.3%, respectively, P = 0.19). Multiple secondary clinical endpoints were significantly worse in the milrinone group, including sustained hypotension requiring intervention (10.7% versus 3.2%, P < 0.001) and new atrial arrhythmias (4.6% versus 1.5%, P = 0.004) (16).

Despite these negative findings, milrinone, dobutamine, and dopamine continue to be used relatively frequently in the management of ADHF, especially when more conservative therapies fail. Therefore, the preponderance of evidence indicates that β-agonists and phosphodiesterase inhibitors should typically be avoided in ADHF or limited to short-term, palliative use.

What to do with long-term β-blocker therapy in the setting of ADHF remains a clinical conundrum (94). The β-blocker therapy should be decreased by about half in patients with evidence of hypoperfusion, and stopped in patients with frank cardiogenic shock. There is, however, little evidence to support this recommendation.

5. Aquaretics
Since in HF there is nonosmotic stimulation of the AVP release, which can lead to hyponatremia, V2 receptor antagonists have been used in patients with ADHF. In a double-blind, placebo-controlled dose-ranging study of ACTIV in CHF (58), 319 patients were randomized to three different doses of tolvaptan. Patients randomized to tolvaptan did not suffer any electrolyte abnormalities, worsening renal function, or hypotension. However, after 60 d there was no significant difference among the HF patients randomized to tolvaptan versus placebo. A post hoc analysis, however, demonstrated that mortality was lower in patients with renal dysfunction or severe systemic congestion who were randomized to tolvaptan. This finding led to EVEREST, which evaluated the short- and long-term efficacy and safety of tolvaptan added to optimal medical management in patients with worsening heart failure (59). In the short term, tolvaptan decreased body weight, but over the 9.9 mo of the study there was no difference in all-cause mortality, cardiovascular death, or hospitalization between tolvaptan and the placebo. There were no differences in renal function or side effects between the two groups.

Future Therapy of ADHF
A1-adenosine antagonists. Another promising new class of therapeutic agents is the A1-adenosine receptor antagonists. Plasma adenosine concentration is elevated in patients with HF, with rising levels as the severity of the disease increases (95). Adenosine binding to A1 receptors causes vasoconstriction of the afferent arteriole, decreased renal blood flow and GFR, and enhanced sodium reabsorption by the proximal tubule. Antagonism of A1-adenosine receptors thus has the potential to improve renal function and reverse diuretic resistance in patients with HF (38,96,97). There are results in HF that demonstrate that A1-adenosine receptor antagonism preserves renal function while simultaneously promoting enhanced response to loop diuretics. Large-scale, randomized controlled
trials are required to examine the long-term benefit of A1-adenosine receptor antagonism.

**Ultrafiltration.** Peripheral ultrafiltration is a promising treatment option for patients with ADHF. The ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial involved 200 patients with ADHF and showed that peripheral ultrafiltration compared with diuretics alone improved weight loss at 48 h (5.0 versus 3.1 kg, \( P < 0.001 \)), decreased the need for vasoactive drugs (3% versus 13%, \( P = 0.02 \)), and reduced the rate of readmission to hospital at 90 d (18% versus 32%, \( P = 0.02 \)) (98). Yet, there was a nonstatistically significant trend toward increased Cr in patients who were treated with ultrafiltration. It is not known if ultrafiltration would demonstrate such beneficial effects as compared with diuretics for comparable negative fluid balance. With diuretic resistance, ultrafiltration may be the only therapeutic approach available, unless it can be reversed with mineralocorticoid antagonism.

**Levosimendan (as a novel inotrope).** Levosimendan binds to cardiac troponin C, stabilizing the conformational change of troponin C through binding to calcium, thereby improving cross-bridging and contractility (99). In the Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE) II study, the investigators demonstrated the efficacy of 24 h of therapy with this drug compared with placebo. The patient population studied in this trial included ADHF patients with ejection fraction <30% and dyspnea at rest despite therapy with diuretics (100). After a 5-d followup, the investigators found the clinical improvement was 33% higher in the levosimendan group and the clinical deterioration was 26% lower than in the placebo group. However, there was an important safety concern in regard to a trend toward increased mortality in those who received levsimendan (101) (Table 1). Levosimendan is currently used in Europe, but due to safety concerns has not been approved by the Food and Drug Administration in the United States.

**Conclusion**

The ADHF is a complex and diverse pathophysiologic state manifested by concomitant heart and kidney failure, worsening renal function during ADHF treatment, and diuretic resistance in the setting of persistent congestion. The challenge is to understand the pathophysiology of this complex syndrome. There are multiple pathophysiological pathways involved. Without targeting the kidney, and taming the neurohormonal storm, the outcome of ADHF continues to be grave.

**Disclosures**

None.

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