CHAPTER 118

Principles of Diuretic Management in Heart Failure

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OBJECTIVES

This chapter will:

1. Explain the negative effects of extra cellular fluid volume expansion on cardiac and renal function.
2. Explain how heart failure and chronic kidney disease contribute to diuretic resistance.
3. Identify risk factors for worsening renal function in acute decompensated heart failure.
4. Describe combination diuretic therapy in acute decompensated heart failure.

Heart failure (HF) currently affects approximately 26 million adults worldwide, including 15 million in Europe and 5.7 million in the United States.[1] The worldwide cost of HF is estimated to be $108 billion per year.[2] Among those admitted to the hospital with HF, approximately 25% in the United States are readmitted within 30 days, whereas 31.9% in Europe are readmitted within 1 year.[1,3] Of patients readmitted,14% to 30% are due to HF.[4] Studies have shown that patients frequently are discharged from the hospital with elevated filling pressures (intravascular volumes).[5] Fluid overload not only contributes to hospital readmissions but also negatively affects myocardial and renal performance.[6]

Congestive symptoms of dyspnea, abdominal fullness, and edema are some of the most common clinical manifestations of HF. Diuretics remain one of the most important therapies in HF because they improve congestive symptoms and, in some cases, improve organ function. Despite the benefits of diuretics, studies have shown increased mortality in HF patients treated with diuretics, particularly in high doses. Resistance to diuretic therapy is a common problem in patients with HF and is associated with increased mortality. In addition, diuretics may be associated with worsening renal function in HF patients. Chronic kidney disease (CKD) commonly coexists with HF and contributes to diuretic resistance and increased mortality. The normal counterregulatory responses to diuretics are aggravated by neurohormonal changes of HF, further contributing to diuretic resistance. Appropriate diuretic management in HF requires an understanding of diuretic resistance, mechanisms of perturbations in renal function during diuretic treatment, and an understanding of the pharmacology of diuretics.

CONSEQUENCES OF EXTRACELLULAR FLUID VOLUME EXPANSION

Fluid overload causes a number of abnormalities in the heart. Progressive fluid overload and consequent ventricular dilatation cause dilatation of the mitral valve annulus and malcoaptation of the leaflets.[7] As a consequence, mitral regurgitation increases and forward ejection decreases. Ventricular dilatation also increases myocardial wall stress, which increases myocardial oxygen demand and can contribute to myocardial ischemia.[8] Furthermore, progressive volume overload can lead to a leftward shift of the interventricular septum. Septal shift causes a reduction in left ventricular (LV) cavity size, reduced LV filling and thus a reduction in cardiac output.[9]

Fluid overload also can compromise renal function directly. Elevation of right-sided filling pressures (right atrial pressure, central venous pressure) leads to elevation in renal venous pressure. Using isolated dog kidneys perfused by a heart lung apparatus, Winton showed that increases of venous pressure to more than 20 mm Hg caused decreased renal blood flow, increased blood urea nitrogen, decreased urine volume, and decreased urine sodium excretion.[10] Importantly, the lower the mean arterial pressure, the lesser was the increase in venous pressure required to reduce urine volume. Using isolated, perfused rat kidneys, Firth showed that an increase of venous pressure of at least 12.5 mm Hg reduced urine Na excretion, where as a venous pressure of at least 25 mm Hg reduced glomerular filtration rate (GFR).[11] Increased renal venous pressure in intact dogs has been shown to reduce urine sodium excretion.[12,13] Maxwell showed that increased renal venous pressure was associated with decreased GFR in HF patients.[14] In a study of patients with pulmonary hypertension, right atrial pressure showed a significant negative correlation with GFR.[15] In a study of patients undergoing right heart catheterization, a significant negative correlation was found between central venous pressure (CVP) exceeding 6 mm Hg and estimated GFR.[16] Mullens showed that a higher admission CVP was associated with the development of worsening renal function (WRF) in patients with acute decompensated heart failure.[17]

Increases in intraabdominal pressure sometimes are seen in advanced HF and can affect renal function. Experimental increases in intraabdominal pressure (IAP) to 20 mm Hg reduce the GFR by more than 25%.[18] In a study of patients with acute decompensated heart failure (ADHF), elevated IAP was associated with increased baseline creatinine; there was a significant positive correlation between reductions in intraabdominal pressure and reductions in serum creatinine.[19]

PHYSIOLOGIC RESPONSE TO DIURETICS

The normal physiologic response to a diuretic leads to a decrease in the effect of the diuretic over time. Inhibition of sodium chloride reabsorption in the thick ascending limb of Henle (TALH) by loop diuretics causes a significant increase in the delivery of sodium chloride to the distal convoluted tubule (DCT). Studies have demonstrated a load-dependent increase in DCT sodium reabsorption in response to a bolus of furosemide.[20] Once the tubular diuretic concentration falls below its threshold concentration, a period of sodium retention begins. Mechanisms of postdiuretic sodium retention include extracellular fluid volume (ECFV) depletion, increased TALH sodium reabsorption (caused by increased NKCC transporter number and activity), and increased DCT sodium reabsorption (caused by increased sodium chloride transporter number).[20] Finally, chronic diuretic use leads to progressively less natriuresis for any given diuretic dose. This response has been termed the "braking phenomenon." ECFV depletion is necessary for the braking phenomenon to occur.[20] Depletion of the ECFV causes stimulation of sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS). SNS stimulation and angiotensin II increase proximal tubular sodium reabsorption as well as increase the filtration fraction.[21–23] An increase in filtration fraction results in greater proximal tubular fluid reabsorption owing to increases in peritubular capillary oncotic pressure. Norepinephrine and angiotensin II reduce renal blood flow, thus reducing the filtered load and excretion of sodium. Aldosterone causes increases in collecting duct sodium reabsorption, which further reduces urine sodium excretion. Finally, the chronic administration of loop diuretics leads to hypertrophy and hyperplasia of the DCT, which further increases sodium reabsorption and contributes to the braking phenomenon.[24,25] This DCT hypertrophy depends on increased sodium chloride delivery and increased serum aldosterone.[26]

INFLUENCE OF HEART FAILURE ON DIURETIC RESPONSIVENESS

In HF, arterial underfilling causes baroreceptor activation resulting in increased levels of norepinephrine, renin, angiotensin II, and aldosterone.[27] Consequently, there is a reduction in the filtered load of sodium, an increase in the proximal reabsorption of sodium, decreased distal delivery of filtrate to the nephron, and increased distal sodium reabsorption. All of the above events reduce the available sodium to be excreted by diuretics. Furthermore, in more advanced HF, baroreceptor-mediated vasopressin release causes increased water reabsorption by the nephron. As HF progresses, the degree of arterial underfilling worsens, causing progressive increases in norepinephrine, angiotensin II, aldosterone, and vasopressin. The physiologic responses to HF act synergistically with the normal responses to diuretics, potentially leading to diuretic resistance.

INFLUENCE OF CHRONIC KIDNEY DISEASE ON DIURETIC MANAGEMENT

CKD stage 3 or higher is common in HF with a prevalence 29% to 63%.[28–30] Higher CKD stage is associated with increasing mortality in HF patients.[30,31] Increasing levels of blood urea nitrogen (BUN) and creatinine at admission for ADHF predict greater in-hospital and long-term mortality.[32] In CKD there is a decrease in renal blood flow in addition to a decrease in GFR.[33] Decreases in renal blood flow result in reduced diuretic delivery to the nephron. Diuretics are protein bound and therefore are not filtered at the glomerulus. Diuretics reach the tubular fluid from the peritubular capillaries by secretion through the organic anion transporter in the proximal tubular cells. In CKD, retention of organic anions creates competition for proximal tubular uptake of diuretics.[34] Thus, owing to reductions in renal blood flow and accumulation of organic anions as occurs in CKD, the diuretic dose needed to reach the effective threshold tubular concentration is increased. Finally, impaired renal autoregulation is known to occur in older patients and those with hypertension, atherosclerotic disease, and CKD owing to afferent arteriolar narrowing.[35] Aggressive diuresis and reductions in blood pressure are more likely to lead to worsening renal function in such patients.

BENEFITS OF DIURETICS IN HEART FAILURE

The most obvious benefits of diuretics in HF are their ability to improve patient symptoms.[36] Diuretics relieve dyspnea and abdominal distention and increase exercise capacity. In addition to symptomatic benefits, diuresis affords several physiologic benefits in HF. Intravenous furosemide causes acute reductions in the pulmonary capillary wedge pressure within 5 to 15 minutes; a time before any significant change in urine volume occurs.[37–39] This hemodynamic change results from increases in peripheral venous capacitance. After days of diuresis, increases in stroke volume and decreases in wedge pressure, mean arterial pressure, and systemic vascular resistance are seen.[40] All of these effects are beneficial to those admitted with ADHF. Reduction of filling pressures results in a decrease in the mitral regurgitant orifice and thus decreases mitral regurgitation.[7,41] This reduction in mitral regurgitation leads to increased forward flow, which probably explains, in part, how cardiac output is maintained during diuresis in HF.[42] Diuretic treatment often affects renal function in HF. Of patients admitted with ADHF, 16% to 31% will develop improved renal function in response to diuresis.[43,44] Those who develop improved renal function have more acute kidney injury on presentation as well as more clinical and echocardiographic evidence of right HF.[44]

NEGATIVE EFFECTS OF DIURETICS IN HEART FAILURE

Several retrospective studies have shown that diuretic use in HF is associated with an increased risk of death.[45–48] Studies have shown further that higher diuretic dosages are associated with increased mortality.[46–48] Another study showed that diuretics were associated significantly with an increased risk of arrhythmic death.[45] Ultimately, these studies show an association of diuretics with death but do not prove causation. It is possible, if not likely, that the need for high-dose diuretics is a marker of disease severity in HF, rather than a cause of increased mortality.

HF is associated with elevation of serum renin and aldosterone levels.[27] As HF worsens, renin and aldosterone levels increase progressively[49] and are associated with a worse prognosis.[27] Diuretic treatment in HF causes increases of renin and aldosterone, which has added to concerns that diuretic treatment is harmful in HF.[49,50] Analysis of renin and aldosterone levels from the DOSE-AHF and CARRESS-HF trials showed that changes in renin and aldosterone levels during the trials were not associated with 60-day outcomes of death or rehospitalization for HF.[49] There was no significant difference in renin or aldosterone levels in those treated with high versus low-dose diuretics. Furthermore, ultrafiltration was found to increase renin more than bolus loop diuretic treatment.

Diuretic use in HF is associated with worsening renal function (WRF). WRF occurs in 23% to 36% of patients hospitalized for ADHF.[51–53] WRF during a hospitalization for ADHF predicts greater in-hospital and long-term mortality.[32] Risk factors for WRF included a history of hypertension, SBP exceeding 200 mm Hg, Cr greater than 1.5 mg/dL, BUN greater than 40 mg/dL, and more than basilar rales.[53,54] In the setting of an HF exacerbation, an increase in creatinine of even 0.1 mg/dL increases the risk of mortality and length of hospital stay.[55] It often is assumed that diuretics are the cause of worsened renal function and increased mortality in HF, but other factors may be important.

Patients with HF and more advanced CKD are less likely to be prescribed angiotensin-converting enzyme (ACE) inhibitors.[56] Hospitalized patients with ADHF and progressive renal failure are less likely to be discharged on ACE inhibitors or angiotensin receptor blockers.[29,57] Compared with patients with advanced HF who tolerate an ACE inhibitor, those with circulatory or renal intolerance to an ACE inhibitor have a mortality rate that is 35% higher over 8½ months.[58] Among patients with HF and CKD with a GFR below 40 cc/min, the use of ACE inhibitors was associated with improved survival compared with those who did not use ACE inhibitors.[31] In a study of patients admitted with ADHF, a GFR less than 30 cc/min was associated with a significantly increased risk of death in those not prescribed an ACE inhibitor; the risk of death was not increased significantly in those who were prescribed an ACE inhibitor.[57]

Hypertension is a consistent risk factor for WRF during an admission for ADHF.[53,54,59] In an analysis of the ESCAPE trial, those who developed WRF had a significantly greater reduction in systolic blood pressure (SBP) versus those who did not experience WRF (–10.3 +/– 18.5 vs –2.8 +/– 16 mm Hg, $p < .001$).[60] For every 10 mm Hg SBP decreased, the odds ratio for WRF increased by 1.3 ($p < .001$). The mean doses of hydralazine, nitrates, and ACE inhibitors were significantly greater in the group with greater SBP reduction. In addition, thiazide diuretic use and weight loss were greater in the group with greater SBP reduction. WRF was not associated with an increase in mortality in those who had a significant decrease in SBP, whereas it was associated with a significant increase in mortality in those who did not have a decrease in SBP. Those with WRF who experienced significant hemoconcentration (an indicator of significant diuresis) did not demonstrate an increase in mortality, whereas those who did not experience hemoconcentration did have a significant increase in mortality. Finally, patients who experienced both hemoconcentration and a significant decrease in SBP showed improved survival as compared with the rest of the group.

The same group of investigators performed another analysis of the ESCAPE trial, focusing on the relation between hemoconcentration, WRF, and outcomes.[61] Patients who developed lab evidence of hemoconcentration lost more weight, had greater reductions in filling pressures, and had WRF. Those with hemoconcentration had lower 180-day mortality; this effect persisted after adjustment for baseline patient characteristics. In aggregate, these studies suggest that hemodynamic factors underlie WRF in many patients, and that hemodynamic acute kidney injury (AKI) in ADHF is not associated with a negative prognosis. In fact, the study focusing on hemoconcentration suggests that aggressive diuresis that causes WRF can be associated with improved outcomes. In aggregate, these studies suggest that the cause of WRF is prognostically more important than WRF.

In an analysis of the ESCAPE trial, it was found that patients with ADHF who develop WRF have the same mortality as those who develop improved renal function (IRF).[43] Both groups had increased mortality as compared with patients whose renal function remained stable. Another study of ADHF by the same group also showed that patients with IRF have increased mortality.[44] The increase in mortality seen in the IRF group was restricted to those who redeveloped worsening renal function after hospital discharge. Patients with IRF had more clinical and echocardiographic findings of right HF; filling pressures were not different in those with IRF compared with other patients. Thus improved renal function during ADHF may be a marker for right HF, which may be a marker of poor outcomes.

As can be seen from the above, factors beyond diuretics explain at least some of the excess mortality seen with WRF during ADHF. In particular, the prescription of fewer ACE inhibitors to those with WRF is likely to factor significantly into their poor prognosis. Hemodynamic causes of WRF seem to have a more benign prognosis, whereas those that are not hemodynamic (cardiorenal causes) are associated with increased mortality. Although seemingly counterintuitive, the poor prognosis for some with improved renal function during ADHF (in the context of right HF and recurrent outpatient AKI) further underscores the importance of cardiac function in the determination of mortality.

DIURETIC MANAGEMENT

Loop diuretics are the cornerstone of diuretic management in HF because of their ability to inhibit the highest percentage of the filtered sodium load (Fig. 118.1). Equipotent doses of the three commonly prescribed loop diuretics are equally effective. Although bumetanide and torsemide have an oral bioavailability of 80% to 100%, furosemide has an average oral bioavailability of 50% with a range of 10% to 100%.[62] The potential relevance of diuretic bioavailability was demonstrated in an open label trial of oral torsemide versus furosemide in chronic HF. Patients randomized to torsemide had fewer rehospitalizations for HF compared with the furosemide group.[63] A dose of 40 mg of intravenous (IV) furosemide is equivalent to 20 mg of IV torsemide and 1 mg of IV bumetanide. The maximal effective IV dose of furosemide in patients with HF and normal renal function is 40 to 80 mg.[62] In patients with advanced renal failure, competition for the organic anion transporter decreases the amount of furosemide that reaches the tubular lumen. As a result, higher doses of furosemide must be given as renal function deteriorates. The maximal effective dose of furosemide in a patient with advanced renal and cardiac failure is 160 to 200 mg IV.[62]

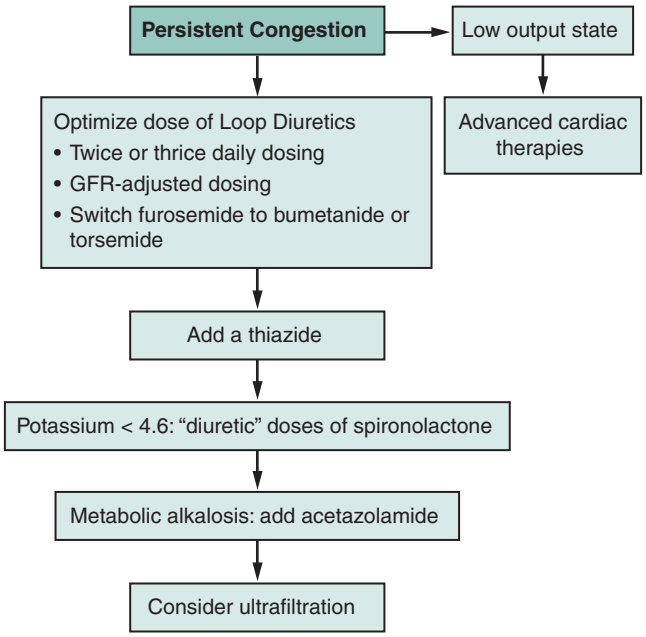

FIGURE 118.1 Stepwise approach to diuretic management in heart failure. *GFR,* glomerular filtration rate.

Administering high-dose loop diuretics as an infusion rather than a bolus can reduce the risk of ototoxicity. Loop diuretics have maximal elimination half-lives that range from 1 hour for bumetanide, to 2 hours for furosemide, to 4 hours for torsemide.[62] Increases of norepinephrine, angiotensin II, and aldosterone in response to loop diuretics result in significant tubular sodium reabsorption during the time the diuretic dose is below its tubular threshold concentration. As such, loop diuretics must be administered multiple times per day to achieve maximal sodium excretion. In an attempt to overcome rebound sodium absorption during the diuretic offset, some practitioners administer loop diuretics as continuous infusion. In a study of patients admitted with ADHF, there was no difference in symptom relief or renal function between those randomized to bolus versus continuous infusion of loop diuretics.[64] In another study of patients with ADHF, compared with bolus loop diuretic therapy, continuous infusion was associated with a higher discharge creatinine, no difference in weight loss, longer length of stay, and higher rates of 6-month readmissions or death.[65]

Resistance to loop diuretics is a common problem in HF. Patients who are resistant to high-dose loop diuretics can benefit from combinations of diuretics that sequentially block sodium reabsorption at different sites along the nephron (Fig. 118.2). In patients who cannot achieve euvolemia with optimal doses of loop diuretics, the addition of a thiazide diuretic can significantly increase natriuresis and weight loss.[66,67] Of the thiazide diuretics, only chlorothiazide is available IV. Thiazide diuretic dosages range from 2.5 to 10 mg daily of metolazone, 25 to 200 mg daily of hydrochlorothiazide, 25 to 100 mg daily of chlorthalidone or 500 to 1000 mg daily of chlorothiazide in single or divided dosages. Studies have shown that thiazide diuretics remain effective in combination with loop diuretics even with a GFR less than 30 cc/min.[68,69] Hypokalemia is a common side effect of combination loop and thiazide diuretic therapy.[66,67] The major role of aldosterone antagonists in ADHF is to mitigate potassium losses resulting from combination loop and thiazide diuretic therapy. The typical dosage of

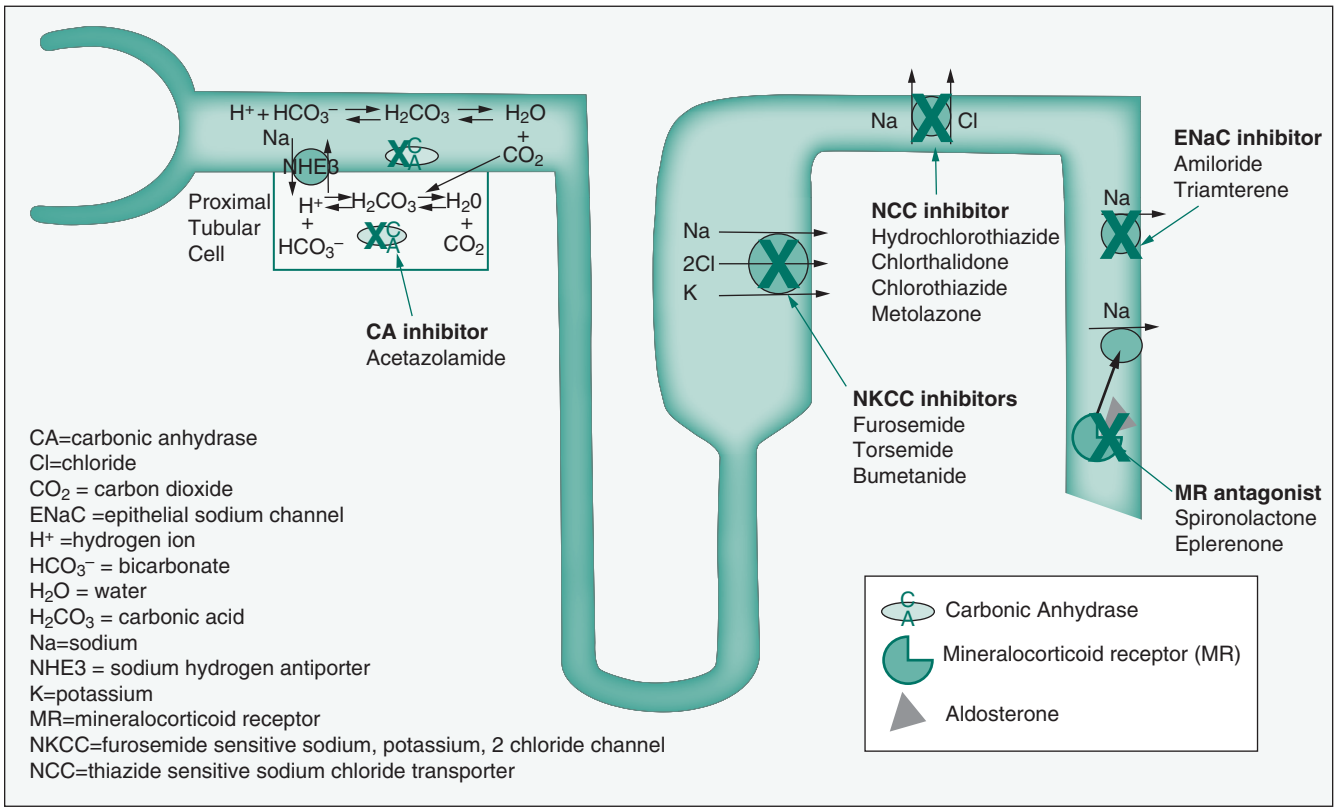

FIGURE 118.2 Diuretics and their sites of action in the nephron.

spironolactone in this setting is 50 to 100 mg daily. The addition of an aldosterone antagonist also can increase sodium excretion and weight loss in patients with ongoing fluid overload despite treatment with high-dose loop diuretics.[70] Metabolic alkalosis is another common complication of loop and thiazide diuretic therapy as a consequence of hypokalemia and hypochloremia. Despite aggressive potassium repletion, metabolic alkalosis persists in some patients. The carbonic anhydrase inhibitor acetazolamide, in doses of 500 to 1000 mg daily, can correct metabolic alkalosis and increase sodium excretion in such patients.[71] Hypokalemia is a potential complication of acetazolamide therapy, particularly in combination with loop and thiazide diuretics. In those who fail combination diuretic treatment, a low cardiac output state or advanced renal failure is likely to be present. If a low cardiac output state is suspected or confirmed, the addition of inotropes may restore diuretic efficacy.[66] The development of AKI in response to diuretics is common in those with ADHF. The differential diagnosis includes true intravascular volume depletion (low cardiac filling pressures with low or normal cardiac output), a low cardiac output state with high filling pressures, cardiorenal syndrome (high filling pressures with normal cardiac output), or removal of volume at a rate that exceeds the rate of capillary refill. In addition to causing AKI, a low cardiac output state also can limit the effectiveness of loop diuretics because of a reduction in the filtered load of sodium and to a reduction in delivery of tubular fluid to the distal nephron. Clues to a low cardiac output state include a proportional pulse pressure of 25% or less, cool extremities, and a systolic blood pressure less than 90 mm Hg; these findings have high specificity, but low sensitivity.[72] In low cardiac output patients, the addition of inotropic support can improve renal function in some cases. History, physical exam, and chest radiography are known to be insensitive for detecting elevated filling pressures, particularly in those lacking edema.[73,74] In some situations it can be challenging to discern between a low cardiac output state with high filling pressures, a normal cardiac output state with high filling pressures, and a normal cardiac output state with low filling pressures. In these patients, a right heart catheterization with direct assessment of filling pressures and cardiac output can clarify the physiologic state and guide further management.

In those who remain fluid overloaded despite optimal doses of loop and thiazide diuretics, and in whom a low cardiac output state has been excluded, ultrafiltration or dialysis is the next step. The routine use of ultrafiltration for volume removal in those with ADHF who are diuretic responsive is not encouraged. In a study of patients with ADHF and cardiorenal syndrome, ultrafiltration resulted in similar weight loss, but a higher incidence of renal failure and serious adverse events as compared with diuretics.[36] In some patients with ADHF and AKI, reduction of filling pressures and relief of renal venous congestion with ultrafiltration can improve renal function and ventricular mechanics such that diuretic responsiveness can be restored.[75]

Currently there are no recommended daily fluid removal goals in HF. Removal of fluid at a rate that exceeds the vascular refill rate could lead to renal failure despite persistently elevated filling pressures. In a study of ultrafiltration in class IV ADHF patients with generalized edema, requiring inotropes, and with AKI, removal of 4880 +/- 896 mL over 9+/- 3 hours (542 cc/hr) did not result in any significant changes in blood pressure, heart rate, or intravascular volume.[75] The plasma refill rate was 14 cc/min at the

beginning of treatment and declined gradually during the course of treatment. In another study of ultrafiltration in patients with treatment-resistant HF, the plasma refill rate was found to be 12.7 mL/min or 762 cc/hr.[76] These data suggest that in ADHF, 4 to 5 L of fluid can be removed safely in a 24-hour period.

BEYOND DIURETICS

Tolvaptan

In a study of patients with ADHF managed with conventional therapy, tolvaptan reduced weight by 0.8 kg versus placebo at day 1 and day 7.[77] In a study of tolvaptan versus placebo in addition to furosemide in ADHF, there was no difference in relief of dyspnea at 24 hours, absence of clinical congestion at 72 hours, length of stay, or 30-day outcomes.[78] Tolvaptan-treated patients had a greater total weight loss at 24 and 72 hours of 1.4 kg and 1.2 kg versus placebo, respectively. Thus, although tolvaptan remains beneficial for hyponatremia, it has no role for primary volume management in HF patients.

Hypertonic Saline and Furosemide

In a study of ADHF, patients randomized to high-dose furosemide and hypertonic saline demonstrated a higher daily urine volume, greater weight loss, lower serum creatinine, and reductions in hospitalization time and hospital readmission rates compared with those treated with high-dose furosemide alone.[79] The mechanism of benefit of the hypertonic saline is unknown but may relate to improving loop diuretic efficacy or better mobilization of fluid into the intravascular space.

Rolofylline

Increased sodium chloride delivery to the macula densa causes release of adenosine, which then binds to the afferent arteriole causing vasoconstriction.[80] This vasoconstriction subsequently decreases GFR. The opposite response occurs because of decreases in sodium chloride delivery to the macula densa. This process, termed tubuloglomerular feedback (TGF), links sodium chloride reabsorption to GFR and thus prevents excessive gains or losses of sodium chloride. Loop diuretics increase sodium chloride delivery to the macula densa but do not elicit a TGF response because they inhibit the NKCC channel.[80] Adenosine is increased in HF patients,[81] and antagonism of adenosine in HF patients was found to augment diuresis resulting from furosemide.[82] Adenosine antagonism also was found to prevent furosemide-induced decreases in GFR. However, in a phase III trial of ADHF, the adenosine antagonist rolofylline did not prevent persistent worsening renal function versus placebo.[83]

SUMMARY

Diuretics remain the most important treatment modality for the relief of congestive symptoms in HF. Beyond symptom relief, diuretics also afford physiologic benefits in HF patients. Although studies have shown that any diuretic use is associated with increased mortality in HF, there is no proof of causality. Alternative explanations such as greater disease severity in patients treated with high-dose diuretics and less prescription of ACE inhibitors in those with WRF may explain the association with mortality. Although diuretic treatment can lead to WRF, studies suggest that WRF resulting from volume contraction or reductions in blood pressure is not associated with negative outcomes. This strengthens the notion that achievement of euvolemia is the paramount concern in HF patients.

Neurohormonal changes in HF compound the normal physiologic response to diuretics and contribute to diuretic resistance. The coexistence of CKD in many HF patients makes diuresis even more challenging. Higher doses of loop diuretics as well as combination therapy with thiazides are required in such patients to achieve euvolemia. An accurate assessment of cardiac output and volume status are essential to the appropriate management of HF patients. Although the routine use of pulmonary artery catheters in HF does not change outcomes and is discouraged,[84] patients with an unclear hemodynamic state may benefit from pulmonary artery catheterization to guide further therapy. Therapies for volume management beyond diuretics have been shown to be ineffective (vaptans, adenosine antagonists) or remain experimental (hypertonic saline and furosemide).

Key Points

1. Increased renal venous pressure is a dominant mechanism of acute kidney injury in acute decompensated heart failure.
2. Increases in creatinine associated with hemodynamics changes (decreased blood pressure, hemoconcentration) are not associated with increased mortality.
3. Patients with chronic kidney disease require much higher doses of loop diuretics.
4. Physiologic renal adaptation to loop diuretics, including increased number and activity of thick ascending limb NKCC and distal tubular NaCl transporters, reduces the efficacy of loop diuretics over time. For this reason, higher doses of loop diuretics, often in combination with thiazides diuretics, are necessary for adequate diuresis.

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