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Practical Applications of Intravenous Diuretic Therapy in Decompensated Heart Failure

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ABSTRACT

Intravenous (IV) loop diuretics play an important role in the treatment of decompensated heart failure (DHF). They inhibit the Na^+-K^+-$2Cl^-$ reabsorptive pump in the thick ascending limb of the loop of Henle, and the resultant natriuresis and diuresis decreases volume load, improves hemodynamics, and reduces DHF symptoms. However, loop diuretics have a short half-life and their efficacy may be limited by postdiuretic sodium rebound during the period between doses in which the tubular diuretic concentration is subtherapeutic. Moreover, they can produce electrolyte abnormalities, neurohormonal activation, intravascular volume depletion, and renal dysfunction. Several studies have reported an association between diuretic therapy and increased morbidity and mortality. In addition, many patients, especially those with more advanced forms of heart failure (HF), are resistant to standard doses of loop diuretics. These high-risk, resistant patients may benefit from pharmacologic and/or nonpharmacologic interventions to improve hemodynamic performance, treatment of renovascular disease, discontinuation of aspirin and other sodium-retaining drugs, manipulation of the route of delivery or combination of diuretic classes, or hemofiltration. Despite >50 years of use, many questions regarding the use of intravenous diuretic agents in patients with DHF are still unanswered, and there remains a compelling need for well-designed randomized, controlled clinical trials to establish appropriate treatment regimens that maximize therapeutic benefit while minimizing morbidity and mortality.

KEYWORDS: Decompensated heart failure; Diuretics; Diuretic resistance; Treatment outcomes

Decompensated heart failure (DHF) is caused by excessive fluid retention or fluid in the wrong place. Many patients with DHF present with dyspnea secondary to pulmonary edema.[1,2] This edema can be managed by reducing volume load using diuretics, reducing pulmonary capillary wedge pressure (PCWP) using vasodilators, increasing alveolar pressure using continuous positive airway pressure devices, or a combination thereof.[3] Of these, intravenous (IV) diuretics are the most commonly employed therapy.[1]

IV diuretics are currently considered the standard of care for volume overload in patients with DHF.[4–7] They relieve symptoms of congestion, reduce intracardiac pressures, and improve cardiac performance.[5,6] As a result, >80% of patients who are hospitalized for DHF receive an IV diuretic.[1] However, despite a >50-year tradition of use, evidence-based data supporting this therapy are lacking.[4–6,8] Only a few randomized, controlled trials of IV diuretic therapy have been performed, and even these data are of limited quality.

RANDOMIZED CONTROLLED TRIALS OF DIURETICS

Two prospective, randomized trials, both conducted nearly 20 years ago, have evaluated the immediate hemodynamic effects of IV diuretics in patients with heart failure (HF) secondary to myocardial infarction.[9,10] In the first trial, Verma and associates[10] compared the effects of an IV diuretic (furosemide, 1 mg/kg), a venodilator (isosorbide dinitrate, 50 to 200 μg/kg per hr), an arteriolar dilator (hydralazine, 0.15 mg/kg), and a positive inotropic agent

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(prenalterol, 50 to 200 μg/kg per hr) as first-line therapy in 48 male subjects with left ventricular dysfunction after acute myocardial infarction. Both furosemide and isosorbide dinitrate reduced left ventricular filling pressure (furosemide by −4 mm Hg, isosorbide dinitrate by −6 mm Hg; both $P < 0.01$) without affecting cardiac output or heart rate. In contrast, both hydralazine and prenalterol increased cardiac output and heart rate but had less effect on left ventricular filling pressure (–2 mm Hg for both drugs; $P < 0.05$). In the second trial, Hutton and colleagues[9] compared the effects of IV furosemide (0.5 mg/kg) and isosorbide 5-mononitrate (15 mg) at the time of routine cardiac catheterization in an unspecified number of patients with left ventricular dysfunction secondary to myocardial infarction. Unlike the first trial, in this trial furosemide induced acute vasoconstriction (PCWP, +6 mm Hg; systolic blood pressure, +20 mm Hg) with a reduction in cardiac output (−0.3 L/min). In contrast, isosorbide 5-mononitrate maintained cardiac output (+0.3 L/min) while reducing both PCWP (−22 mm Hg) and systolic blood pressure (−14 mm Hg). Of note, these trials were too small to assess morbidity or mortality.

Cotter and coworkers[11] assessed the effects of diuretics and nitrates in 104 patients presenting to mobile emergency units with pulmonary edema and signs of DHF. Patients were randomly assigned to treatment with either a low-dose diuretic (furosemide, 40 mg) plus a high-dose nitrate (isosorbide dinitrate, 3-mg bolus every 5 minutes) or a high-dose diuretic (furosemide, 40 mg followed by 80-mg bolus every 15 minutes) plus a low-dose nitrate (isosorbide dinitrate, 1 mg/hr and increased by 1 mg/hr every 10 minutes), and therapy was continued until arterial oxygen saturation was >96% or mean arterial blood pressure had decreased by >30% or was <90 mm Hg. In this trial, the use of high-dose diuretics plus low-dose nitrates was associated with a trend toward increased mortality (6% vs. 2%; $P = 0.61$) and significant increases in the development of myocardial infarction (37% vs. 17%; $P = 0.047$), the need for mechanical ventilation (40% vs. 13%; $P = 0.004$), and the combined end point of death, myocardial infarction, or mechanical ventilation (46% vs. 25%; $P = 0.041$) compared with the use of low-dose diuretics plus high-dose nitrates. However, these data are inconsistent with the experience of others in the general population with acute HF and may reflect only the experience in a small group of exceptionally sick patients. Mechanical ventilation is used for only a small minority of patients with pulmonary edema in most clinical practice, and it is not the experience of others that myocardial infarction develops as a consequence, as opposed to a cause, of DHF.

Although minimal and contradictory evidence exists, IV diuretic therapy is generally accepted for the treatment of patients with DHF; future assessment of this therapy in large-scale, randomized, controlled clinical trials will be difficult.[4] This article reviews what is currently known about the use of diuretics in patients with DHF and makes suggestions regarding the management of patients with diuretic resistance.

STANDARD USE OF INTRAVENOUS DIURETICS

Diuretics differ significantly in their site and mechanism of action.[12,13] Carbonic anhydrase inhibitors inhibit carbonic anhydrase in the proximal tubule. Osmotic agents have an osmotic effect in both the proximal tubule and the thick ascending limb of Henle. Loop diuretics inhibit the Na^+-K^+-$2Cl^-$ reabsorptive pump in the thick ascending limb of the loop of Henle. Thiazide diuretics inhibit electroneutral NaCl reabsorption in the distal convoluted tubule, and potassium-sparing diuretics inhibit Na^+-K^+ exchange in the distal convoluted tubule and collecting duct. With the exception of aldosterone antagonists, diuretics must reach the lumen of the renal tubule to be effective.[12] Osmotic diuretics are directly filtered at the level of the glomerulus and the other diuretics are actively secreted into the tubule using either organic acid or organic base secretory pathways, depending on the diuretic.[12]

Of the various diuretic classes, loop diuretics have the most rapid onset when used intravenously and the most powerful effect when used in high doses.[4,13] In the Acute Decompensated Heart Failure National Registry (ADHERE), 84% of patients received IV furosemide, 7% received IV bumetanide, and 2% received IV torsemide.[1] Similarly, loop diuretics were used at admission in 83% of patients with acute HF in the EuroHeart Survey on Heart Failure II.[14] When used intravenously, the effects of these diuretics are similar, with 40 mg of furosemide equivalent to 20 mg of torsemide or 1 mg of bumetanide.[15–19] Currently, 20 to 100 mg of furosemide, 10 to 100 mg of torsemide, or 0.5 to 4.0 mg of bumetanide are the recommended bolus doses of these diuretics in patients with DHF and moderate-to-severe fluid retention.[4] Failure to respond to adequate doses of one of these diuretics suggests a similar lack of response to other diuretics.[20] It is important to note, however, that the studies used to derive these comparative efficacies typically excluded patients with renal insufficiency (RI), a common comorbidity in patients with HF.[1,4]

Although their efficacy is similar, these 3 agents have noteworthy differences that may influence their use in specific patients. When given orally, torsemide is absorbed faster and/or better than either furosemide or bumetanide, and the higher and more consistent bioavailability leads to a more reliable effect.[20,21] Furosemide is both metabolized and excreted by the kidneys. Consequently, its half-life is prolonged in patients with RI.[20,22] In contrast, both bumetanide and torsemide are primarily metabolized by the liver. Their half-lives are prolonged in patients with liver disease but are unaffected by RI.[20,22] In addition, torsemide has a longer elimination half-life (normal individuals, 3.0 to 4.0 hours; HF patients, 6.0 hours) than either furosemide (normal individuals, 1.5 to 2.0 hours; HF patients, 2.7 hours) or bumetanide (normal individuals, 1.0 hours; HF patients, 1.3 hours), which may reduce the period of postdiuretic sodium rebound absorption (discussed below).[17,19,22,23]

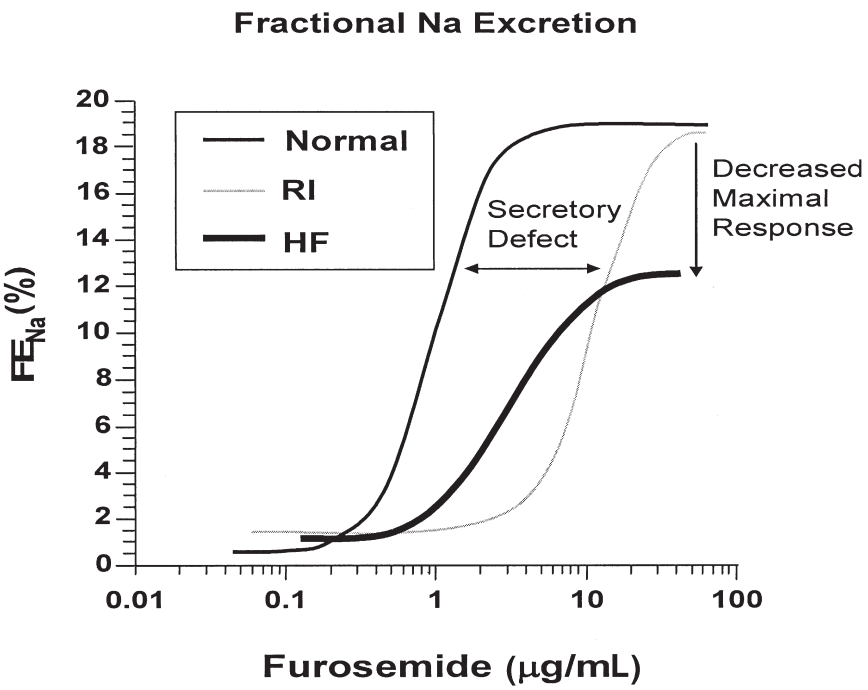

Figure 1 Effect of renal insufficiency (RI) and heart failure (HF) on the dose-response curve for furosemide. FE_{Na} = fractional excretion of sodium. (Adapted with permission from *Cardiology*.[21])

Patient characteristics also have a substantial influence on the efficacy of IV diuretics. Loop diuretics have an S-shaped dose-response curve, and this curve is shifted downward and to the right by HF and other edematous conditions, hypotension, and RI (**Figure 1**),[21] attenuating the maximal response and creating a state of diuretic resistance.[12,13,17,23,24] Several factors are responsible for this shift in the dose-response curve. As alluded to above, achieving a sufficient concentration of the loop diuretic in the thick ascending limb of the loop of Henle is essential for therapeutic efficacy.[17,20] Loop diuretics are actively transported from blood to urine by organic acid secretory pumps in the proximal tubule, and this transport is dependent on the amount of blood reaching these pumps.[17,20] HF, hypotension, and RI all can reduce this blood flow, limiting tubular delivery. As a result, the efficacy of loop diuretics is directly related to creatinine clearance; as creatinine clearance decreases, the dose of loop diuretic needed to produce natriuresis and diuresis must be increased (**Table 1**).[17,20,25] Patients with HF also frequently have elevated arginine vasopressin levels, which mediate increased expression of the Na^+-K^+-$2Cl^-$ reabsorptive pump, potentially blunting the inhibitory effect of loop diuretics on this pump and probably partially responsible for diuretic rebound.[17] Hypertrophy of the distal convoluted tubule, probably mainly in response to chronic diuretic therapy, stimulates increased distal tubular resorption of sodium despite reductions in reabsorption in the loop of Henle with loop diuretics.[23] Finally, high-dose diuretics may have effects on the renal medullary concentration gradient, causing problems with both dilution and concentration of urine.[20,26]

Patient diet, particularly sodium intake, will alter the efficacy of loop diuretics. The half-life of loop diuretics is relatively short (~1 to 4 hours).[17] Following each dose there is a substantial amount of time in which the tubular concentration of the diuretic is subtherapeutic. During this time, sodium resorption can occur (postdiuretic sodium rebound), especially when sodium intake is not adequately restricted, attenuating or completely eliminating the overall diuretic response.[17,22,23,27] In a randomized, crossover evaluation, Wilcox and colleagues[27] evaluated the effect of high (270 mmol/day for 3 days) versus low (20 mmol/day for 3 days) sodium intake on furosemide responsiveness. During periods of low sodium intake, subjects lost a mean of 0.9 kg ($P < 0.01$) and had a mean net negative sodium balance of 146 mmol ($P < 0.001$). In contrast, during periods of high sodium intake, these same subjects lost a mean of 0.2 kg and had a mean net positive sodium balance of 20 mmol (both P = NS) despite a greater diuresis on a high-sodium diet. Thus, the magnitude of diuresis will diminish as the net sodium depletion becomes greater, as the body strives to maintain the balance it is being falsely programmed to achieve. Patients often notice a marked diuresis with the first few doses of diuretic when fluid overloaded but a diminished effect thereafter.

EXPECTED RESPONSE TO INTRAVENOUS DIURETICS

Loop diuretics enhance the excretion of sodium, chloride, potassium, and other ions, increasing urine volume, decreasing intravascular and extracellular fluid, and reducing total body sodium.[20,22,28,29] With bolus therapy, urine out-

Table 1 Doses for continuous intravenous (IV) infusion of loop diuretics

Diuretic	IV Loading Dose	Infusion Rate*†		
		Creatinine Clearance <25 mL/min	Creatinine Clearance 25–75 mL/min	Creatinine Clearance >75 mL/min
Furosemide	40 mg	20 mg then 40 mg/hr	10 mg then 20 mg/hr	10 mg/hr
Torsemide	20 mg	10 mg then 20 mg/hr	5 mg then 10 mg/hr	5 mg/hr
Bumetanide	1 mg	1 mg then 2 mg/hr	0.5 mg then 1 mg/hr	0.5 mg/hr

*Before the infusion is increased, the loading dose should be administered again.
†To achieve creatinine clearance in milliliters per second, multiply by 0.01667.
Adapted with permission from *N Engl J Med.*[20]

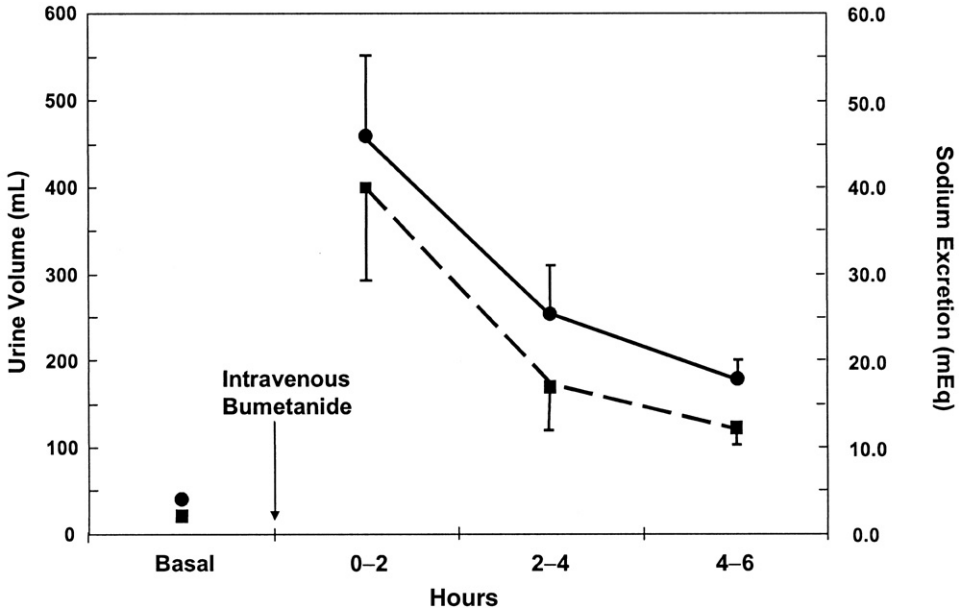

Figure 2 Mean urine volume (*circles*) and sodium excretion (*squares*) after a 1-mg intravenous bolus of bumetanide in 7 spontaneously voiding subjects with heart failure. "Basal" represents the mean urine volume and sodium excretion per 2-hour period in the 24 hours immediately before diuretic administration. Bars represent standard errors. (Adapted from *Int J Clin Pharmacol Ther Toxicol.*[29])

put peaks within 1 to 2 hours and declines to baseline level within 6 hours when assessed using urinary catheters, with changes in sodium excretion mirroring those of urine output (**Figure 2**).[12,29–31]

In healthy volunteers, an IV dose of 40 mg furosemide, 20 mg torsemide, or 1 mg bumetanide produces a maximal response, which is the excretion of 200 to 250 mEq of sodium in 3 to 4 L of urine over a 3- to 4-hour period.[17,20] However, HF significantly blunts these responses. In an evaluation of 10 subjects (mean age, 66 years) with New York Heart Association (NYHA) class III to IV HF, a 20-mg dose of IV furosemide elicited the excretion of 45 mEq of sodium and 24 mEq of potassium in 0.78 L of urine over a 6-hour period.[32] Similarly, a 1-mg dose of IV bumetanide elicited the excretion of 69 mEq of sodium and 21 mEq of potassium in 0.89 L of urine over a 6-hour period in 7 of 9 subjects with HF (mean age, 38 years), and the remaining 2 subjects had no response to IV bumetanide up to a total dose of 3 mg.[29]

POTENTIAL DELETERIOUS EFFECTS OF INTRAVENOUS DIURETICS

Diuretics, and especially their overuse, produce several deleterious effects that can influence clinical outcomes. A frequent consequence of diuretic therapy is electrolyte disturbances.[4,6,13,20,22] Loop diuretics increase urinary excretion of potassium, magnesium, and calcium, reducing total body stores of these essential cations, causing secondary hyperparathyroidism, and potentially increasing the risk of arrhythmic mortality.[20,22,33,34] Patients with advanced HF and long-term furosemide usage have elevated parathyroid hormone levels and associated moderate-to-marked reductions in bone mineral density.[34] In addition, reduction in cytosolic free magnesium increases intracellular calcium loading, and reduction of magnesium in circulating mononuclear cells produces a proinflammatory phenotype.[34]

Diuretics can cause intravascular volume depletion, leading to hypotension, diminished cardiac output, re-

duced glomerular filtration rate (GFR), and renal dysfunction.[4,13,22,26,35–38] In a prospective, randomized evaluation of 33 patients in the intensive care unit who had pulmonary edema or fluid overload, aggressive diureses with either bolus or continuous-infusion furosemide therapy produced a significant reduction in mean arterial pressure (bolus, −13 mm Hg; 95% confidence interval [CI], −5 to −21 mm Hg; and continuous infusion: −16 mm Hg; 95% CI, −9 to −24 mm Hg) and an increase in mean serum creatinine levels (bolus, +0.23 mg/dL; 95% CI, +0.01 to +0.45 mg/dL; and continuous infusion, +0.14 mg/dL; 95% CI, −0.03 to +0.31 mg/dL [1 mg/dL = 88.4 μmol/L]).[38] In 20 patients with severe HF, a continuous infusion of furosemide (mean daily dose, 690 mg) produced a 5% increase in mean serum creatinine level ($P < 0.01$).[36] In 20 subjects with refractory HF, use of medium-dose (5 mg/kg per day) and high-dose (10 mg/kg per day) IV furosemide was associated with 14% ± 8% and 15% ± 6% reductions in mean arterial pressure and 41% ± 23% and 42% ± 23% reductions in creatinine clearance, respectively, with the reduction in creatinine clearance correlated directly with the reduction in blood pressure ($r = 0.7$; $P = 0.007$).[26] In a randomized, double-blind evaluation of patients with symptomatic HF, IV administration of 80 mg furosemide produced a 7.4-mm Hg decline in systolic blood pressure and a 17.3% decline in GFR, compared with a 1.4-mm Hg increase in systolic blood pressure and a 2.5% increase in GFR following IV placebo administration.[37] Finally, in a nested case-control study of 382 subjects hospitalized for HF, use of loop diuretics was associated with a significant increase in the risk of worsening renal function (odds ratio [OR], 1.04 per 20-mg furosemide equivalent received during the preceding day; 95% CI, 1.004 to 1.076; $P = 0.03$).[35]

Diuretics cause adverse neurohormonal activation.[39–44] In 10 patients with HF, mean plasma renin, aldosterone, and angiotensin II activity increased within 30 minutes following a 1-mg/kg bolus of IV furosemide (although only the change in angiotensin II activity was statistically significant), and these elevations persisted in 4 patients receiving chronic furosemide administration.[42] In 15 patients with chronic HF, furosemide produced acute vasoconstriction with significant increases in plasma renin and norepinephrine levels within 10 minutes of IV administration (**Figure 3**).[44] Similarly, in 8 patients with NYHA class II to III HF, plasma renin activity increased 170%, aldosterone activity increased 40%, and norepinephrine activity increased 40% (all $P < 0.01$) in the 2-hour period immediately following IV administration of furosemide (mean dose, 248 mg).[39] These hormone levels remained elevated for the next 4 days and were associated with fluid retention, leading to the return of elevated filling pressures, and reoccurrence of pulmonary congestion.[45]

Although large, prospective, randomized clinical trials of diuretic therapy are lacking, data are available that suggest increased morbidity and mortality with both acute and chronic diuretic therapy.[33,46–49] Use of long-term oral non–potassium-sparing diuretics was associated with a 1.33-fold (95% CI, 1.05 to 1.69; $P = 0.02$) increase in the risk of arrhythmic death after controlling for other mortality risk factors in the Studies in Left Ventricular Dysfunction (SOLVD) trial.[33] This may reflect potassium and magnesium depletion or activation of neuroendocrine systems—particularly the sympathetic nervous system.[45] In the Prospective Randomized Amlodipine Survival Evaluation (PRAISE), chronic use of high-dose diuretics (>80-mg/day furosemide equivalents) was associated with a significant increase in all-cause mortality (hazard ratio [HR], 1.37; $P = 0.004$), sudden death (HR, 1.39; $P = 0.04$), and pump failure death (HR, 1.51; $P = 0.03$), after adjusting for relevant covariates.[48] Similarly, in an evaluation of 552 patients with acute renal failure, 117 (21%) of whom had HF, acute use of diuretics was associated with an increase in both inhospital mortality (OR, 1.68; 95% CI, 1.06 to 2.64) and the combined end point of death or failure of renal function to recover (OR, 1.77; 95% CI, 1.14 to 2.76), after adjusting for relevant covariates and propensity score.[47] As in the PRAISE evaluation, this increased risk was sustained primarily by patients who were relatively unresponsive to therapy and who therefore received high-dose diuretics. In an evaluation of data from >55,000 DHF hospitalizations in the ADHERE registry, use of IV diuretics was associated with an increased risk of intensive care unit stay >3 days (OR, 1.59; 95% CI, 1.26 to 2.00; $P < 0.001$), total length of hospital stay >4 days (OR, 1.49; 95% CI, 1.40 to 1.58; $P < 0.001$), and inhospital mortality (OR, 1.29; 95% CI, 1.04 to 1.59; $P = 0.02$), after adjusting for relevant covariates and propensity score.[46] Finally, in an evaluation of 1,216 ambulatory patients with chronic HF, predictors of worsening renal function included vascular disease, use of thiazide diuretics, and baseline urea >9 mmol/L.[49]

FAILURE TO RESPOND TO STANDARD DIURETIC DOSES

Diuretic resistance, i.e., the failure to adequately respond to standard doses of diuretics, is a major issue in the management of patients with advanced HF. It is frequently seen in patients with severe symptoms, hypotension, hyponatremia, renal dysfunction, and/or significant cardiac dysfunction, and it has been associated with increased mortality.[23,47,48,50]

Currently, the management of patients with diuretic resistance must be guided by the available limited data and theoretical considerations. Despite the significance of this disorder, large-scale randomized clinical trials have not yet been performed, and there are no evidence-based guidelines available.

Since loop diuretics are dependent on glomerular filtration to reach their site of action in the kidney, their efficacy is diminished by anything that reduces GFR. One of the most important determinants of renal blood flow is glomerular perfusion pressure,[22] which can be reduced by both low arterial blood pressure and renal artery stenosis. Stopping

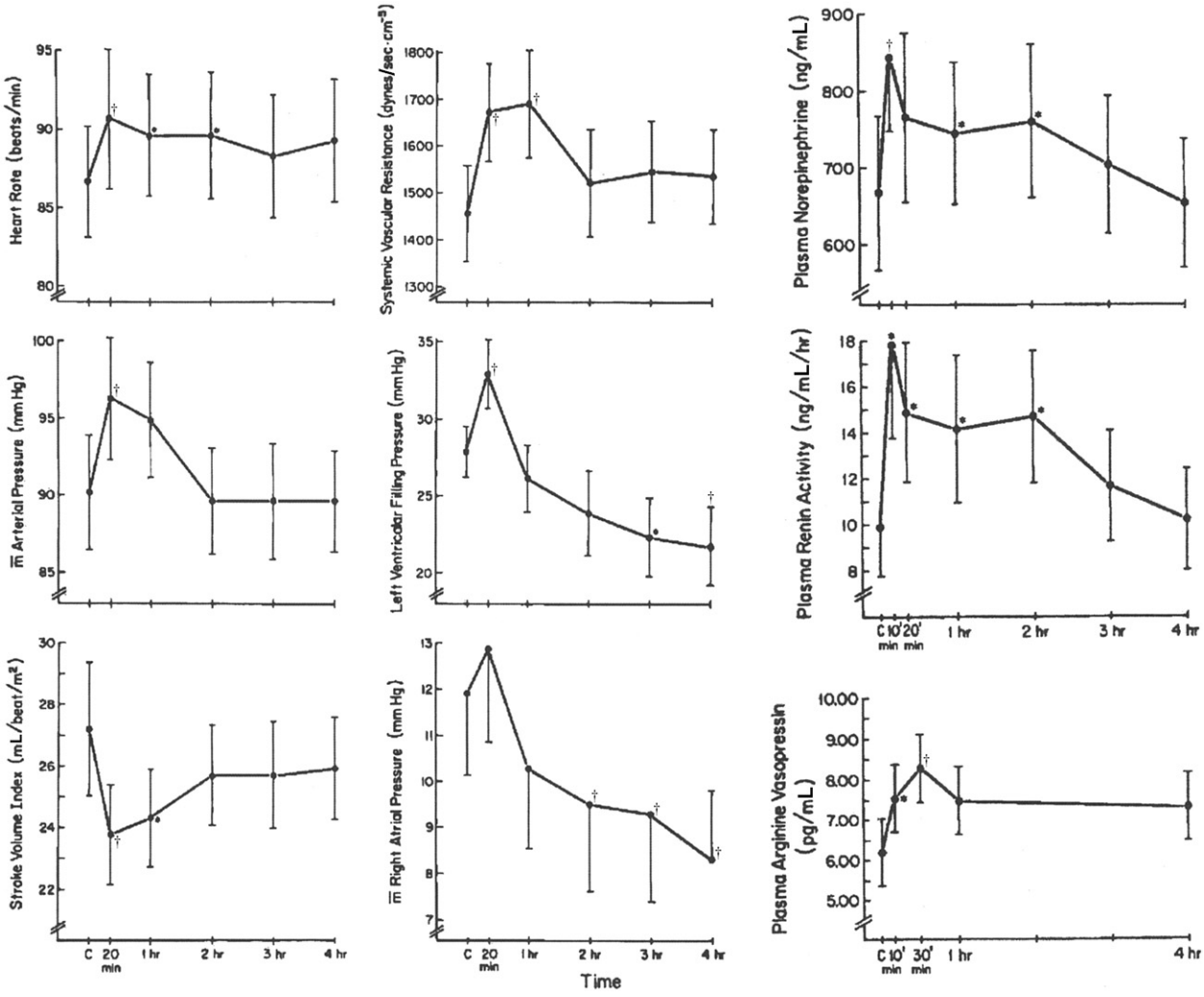

Figure 3 Acute hemodynamic and neurohormonal response to intravenous furosemide in 15 patients with chronic heart failure. "C" = control period before administration of furosemide. Circles represent mean values. Bars for arginine vasopressin represent standard deviations; all other bars represent standard errors. $^{*}P < 0.05$; $^{\dagger}P < 0.01$. (Adapted with permission from *Ann Intern Med.*[44])

nonessential vasodilators (for instance, calcium antagonists and α-blockers) may allow an increase in blood pressure. Reducing diuretics to increase blood pressure in this setting usually is not possible.[13,22,24,26] In a recent evaluation of 54 patients with severe HF, lower systolic and diastolic blood pressures increased the risk of diuretic resistance ($P < 0.05$ and $P < 0.01$, respectively).[24] It is important to note, however, that although angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers can reduce blood pressure, they have proven benefit in cardiovascular and renal disease[51–55] and should be withdrawn only as a last resort. Renal artery stenosis is a common and often overlooked cause of reduced renal blood flow in patients with HF.[56] Approximately 33% of patients with HF have significant renovascular disease.[57] In these individuals, angioplasty, with or without stenting, may be beneficial. Successful renal revascularization reduced elevated blood pressure and improved renal function and virtually eliminated pulmonary edema in a small case series of 11 patients with renovascular disease and pulmonary edema.[58] Similarly, in 39 patients with HF and renal artery stenosis, renal artery stenting significantly reduced HF hospitalizations, by 88% ($P < 0.001$), and produced a trend toward improvement in renal function.[59] However, renal revascularization is not without risk and in some patients leads to worsening renal function.[59,60] Consequently, the risk–benefit ratio of renal revascularization is unclear and is currently being evaluated in the Angioplasty and Stent for Renal Artery Lesions (ASTRAL) trial.[61] A substudy of this trial is assessing the effect of renal revascularization specifically in HF patients.

Finally, the possible effect of concomitant medications on diuretic responsiveness should be considered. Specifically, is the patient receiving aspirin and/or a nonsteroidal anti-inflammatory drug (NSAID), and if so, can these be discontinued? Within minutes of IV administration, furosemide produces venodilation that is similar in degree to that caused by nitroglycerin.[62–65] Aspirin[64] and NSAIDs[63,65] block this response. In addition, aspirin and NSAIDs block the increase in renal blood flow that is caused by loop diuretics.[31] In a crossover evaluation of 10 patients with HF, oral NSAID administration

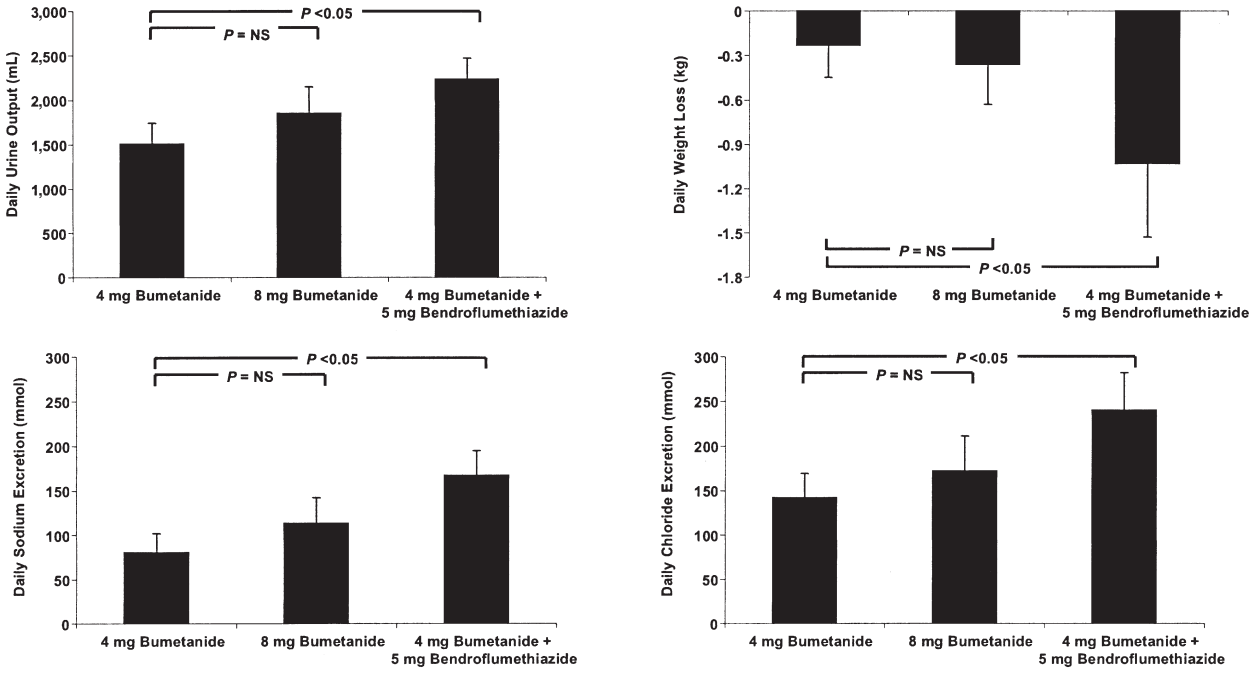

Figure 4 Effect of adding a thiazide diuretic (bendroflumethiazide) compared with doubling the dose of the loop diuretic (bumetanide) on urine output, weight loss, sodium excretion, and chloride excretion in 6 patients with heart failure requiring more intensive diuretic therapy. Bars represent standard errors. (Adapted from *Am Heart J.*[82])

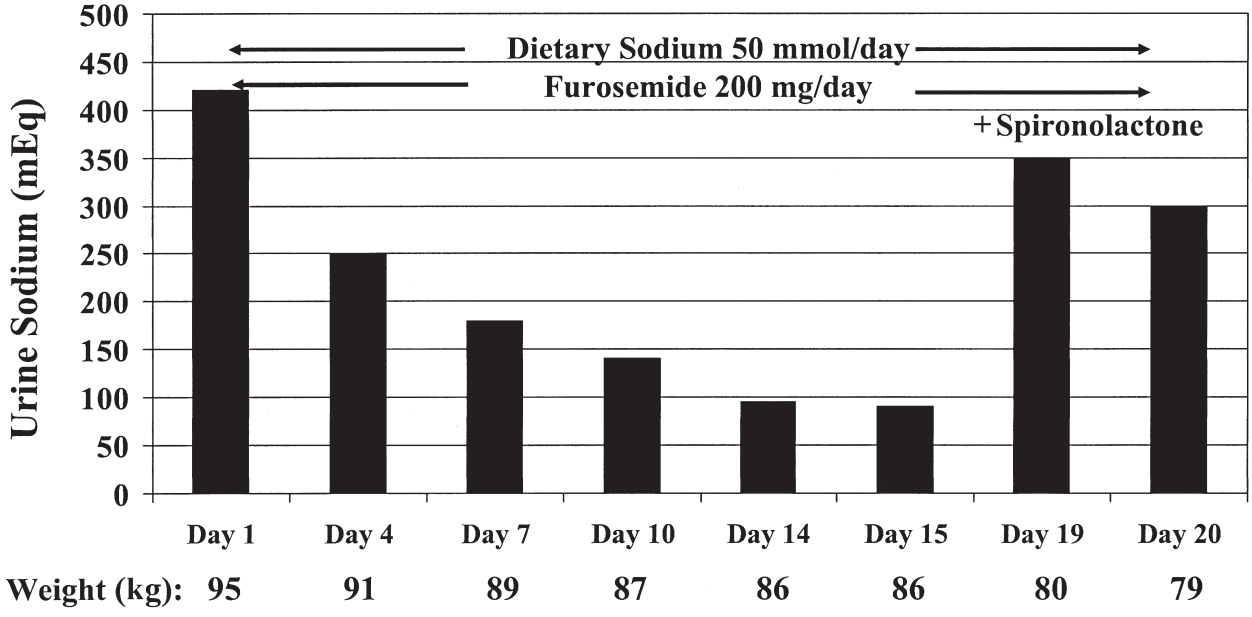

Figure 5 Effect of adding spironolactone to furosemide in a patient with heart failure unresponsive to ordinary diuretic therapy (1 mmol/L = 1 mEqL). (Adapted from *BMJ.*[83])

produced a 40% (95% CI, 11% to 59%) reduction in GFR compared with placebo.[66] Two substantial studies (Warfarin and Aspirin in Heart Failure [WASH] and Warfarin and Antiplatelet Trial in Chronic Heart Failure [WATCH]) have shown that up to 33% of HF hospitalizations may be owing to the use of low-dose aspirin for cardiovascular prophylaxis.[67,68] In addition, edema is a recognized side effect of thiazolidinediones, particularly when combined with insulin. Both patients with HF and clinicians must be cognizant of the risks of using these agents.[69]

If addressing these issues does not resolve the resistance, then a change in diuretic regimen should be considered. Although equipotent doses of loop diuretics should have equivalent efficacy, this may not be true in individual patients owing to differences in oral absorption and half-life. Switching from furosemide to torsemide, with its improved

Table 2 Mechanisms of diuretic resistance and therapeutic interventions

	Interventions	
Target	Preferred Strategy When Possible	Alternative
Cardiac dysfunction	• Improve the underlying cardiac problem — Discontinue cardiodepressant drugs (e.g., flecainide, verapamil) — Pharmacologic (e.g., implement long-term β-blocker) — Valve repair/replacement — Cardiac resynchronization — Revascularization of hibernating myocardium — Surgical ventricular remodeling	• Replace cardiac function — Left ventricular assist device — Cardiac transplantation
Renal dysfunction	• Restore renal/glomerular perfusion pressure — Reduce diuretic if possible — Reduce nonessential vasodilator — Cardiac resynchronization — Treat renovascular disease — Counterpulsation	• Circumvent renal function — Dialysis
Sodium-retaining agents	• Discontinue use, if possible — Stop aspirin or switch to anticoagulant — Switch from NSAIDs to simple analgesia — Stop glitazone	
Diuretic therapy	• Intensify diuretic regimen — Switch from furosemide to torsemide — Switch from bolus to continuous infusion — Add diuretic from a different class • Loop + thiazide • Loop + aldosterone antagonist — Natriuretic peptide analogues?	• Circumvent need for diuresis — Sodium restriction — Ultrafiltration

NSAIDs = nonsteroidal anti-inflammatory drugs.

absorption and longer elimination half-life, should improve efficacy.[17,22,23] Another potential way to reduce postdiuretic sodium rebound and improve the efficacy of loop diuretics is to change from intermittent boluses to a continuous infusion.[4,13,20,31,70] Although a neutral effect has been seen in some studies,[71,72] most report improved efficacy with continuous-infusion diuretic therapy.[30,36,38,73–77] However, continuous-infusion therapy may be less easy for the nursing staff to administer and monitor and may be associated with a not insubstantial rate of infusion-site thrombophlebitis and infection, though it does reduce the risk of ototoxicity by eliminating the high peaks in drug level that occur with bolus therapy.[36] Lastly, addition of a diuretic with a different site and mechanism of action may improve diuretic efficacy.[13,20,23,78–84] Chronic administration of loop diuretics increases sodium delivery to the distal tubule, ultimately stimulating enhanced resorptive capacity in this tubule, which limits the drugs' effectiveness.[79] Both potassium-sparing and thiazide-type diuretics inhibit this distal-tubular resorption, improving overall diuretic responsiveness.[12,79] For example, the addition of metolazone to IV furosemide produced clinical improvement in 12 of 17 (71%) patients hospitalized for NYHA class IV HF who were refractory to conventional therapy.[80] Similarly, adding a thiazide diuretic was more efficacious than doubling the loop diuretic dose in a permutation trial of 6 subjects with HF requiring more intensive diuretic therapy (**Figure 4**).[82] It is important to remember that, similar to loop diuretics, thiazide diuretics must reach the lumen of the nephron to be effective. Consequently, the dose of thiazide diuretics must be increased in patients with RI.[20]

Increases in aldosterone may lead to sodium retention and hypokalemia even when patients are receiving ACE inhibitors. High-dose spironolactone (200 mg/day) can exert a powerful diuresis (**Figure 5**).[83] Aldosterone receptor antagonists appear especially effective in patients with "right-sided" failure and hepatic congestion, reflecting an impaired ability to metabolize aldosterone rather than increased excretion. It is uncertain whether low-dose aldosterone receptor antagonists exert similar diuretic effects. Failure to lose body weight on long-term low-dose aldosterone receptor antagonists may reflect an increase in lean body mass with the prevention of cachexia and may obscure a reduction in salt and water load.

When diuretic resistance persists, hemofiltration should be considered. In patients with moderate-to-severe HF, hemofiltration improves symptoms, hemodynamics, urine output, and diuretic responsiveness.[39,80,85–88] Moreover, unlike loop diuretics, hemofiltration does not activate the macula densa and, consequently, produces less long-term neurohormonal activation.[13,39,85,87] Ideally, it should be started early in the management of refractory diuretic resistance because

it is potentially less efficacious when used as a last resort.[89] **Table 2** summarizes the various mechanisms for the development of diuretic resistance and possible interventions to address these mechanisms.

SUMMARY

IV loop diuretics are considered the standard of care in patients with DHF. They decrease volume overload, improve hemodynamics, and reduce symptoms. However, they also can produce electrolyte abnormalities, neurohormonal activation, intravascular volume depletion, and renal dysfunction, leading to increased morbidity and mortality. In addition, many patients are resistant to the effects of standard doses of loop diuretics. These patients may benefit from the reduction or elimination of factors contributing to the resistance, alteration of the diuretic regimen, or initiation of hemofiltration. Despite >50 years of use, there remains a compelling need for well-designed, randomized, controlled clinical trials of diuretic therapy in patients with DHF to establish appropriate treatment regimens that maximize therapeutic benefit while minimizing morbidity and mortality.

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