

Review

Pathophysiology of Diuretic Resistance and Its Implications for the Management of Chronic Heart Failure

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Abstract—Diuretic resistance implies a failure to increase fluid and sodium (Na⁺) output sufficiently to relieve volume overload, edema, or congestion, despite escalating doses of a loop diuretic to a ceiling level (80 mg of furosemide once or twice daily or greater in those with reduced glomerular filtration rate or heart failure). It is a major cause of recurrent hospitalizations in patients with chronic heart failure and predicts death but is difficult to diagnose unequivocally. Pharmacokinetic mechanisms include the low and variable bioavailability of furosemide and the short duration of all loop diuretics that provides time for the kidneys to restore diuretic-induced Na⁺ losses between doses. Pathophysiological mechanisms of diuretic resistance include an inappropriately high daily salt intake that exceeds the acute diuretic-induced salt loss, hyponatremia or hypokalemic, hypochloremic metabolic alkalosis, and reflex activation of the renal nerves. Nephron mechanisms include tubular tolerance that can develop even during the time that the renal tubules are exposed to a single dose of diuretic, or enhanced reabsorption in the proximal tubule that limits delivery to the loop, or an adaptive increase in reabsorption in the downstream distal tubule and collecting ducts that offsets ongoing blockade of Na⁺ reabsorption in the loop of Henle. These provide rationales for novel strategies including the concurrent use of diuretics that block these nephron segments and even sequential nephron blockade with multiple diuretics and aquaretics combined in severely diuretic-resistant patients with heart failure.

Key Words: diuretics ■ edema ■ furosemide ■ heart failure ■ torsemide

We review the pathophysiology of diuretic resistance and its implications for improving the management of patients with chronic heart failure (CHF). Diuretic resistance is a failure to increase fluid and sodium (Na⁺) output sufficiently to relieve volume overload, edema or congestion despite a full dose of a loop diuretic. More quantitative definitions include a failure of oral furosemide (160 mg twice daily or equivalent) to increase Na⁺ excretion by at least 90 mmol over 3 days.¹ Alternatively, a spot urine sample obtained 1 to 2 hours after a loop diuretic can be used to predict Na⁺ output. A Na⁺ output <50 mmol is generally insufficient to induce a negative Na⁺ balance with loop diuretics and therefore predicts diuretic resistance. This was validated prospectively in 50 patients²:

Na⁺ output (mmol)=estimated glomerular filtration rate (eGFR) (body surface area/1.73) (S_{Cr}/U_{Cr})×60 min×3.25 h×(U_{Na}/1000 mL) where Cr is urine or serum creatinine and U_{Na} is urine sodium concentration.²

A poor diuretic response predicts subsequent death, readmission, or renal complications from CHF.³ Recognition of diuretic resistance is hampered by imprecise metrics. Intravenous diuretics for patients hospitalized with decompensated HF can reduce body weight by 11 kg yet signs of hypervolemia and congestion persist in >50% and blood volume, that predicts mortality,⁴ remains ≈30% expanded.⁵ Thus, interstitial fluid, including peripheral and pulmonary edema, is depleted selectively but blood volume is well defended. Indeed, >85% of fluid removed by

diuretics is from extravascular sites that include peripheral and pulmonary edema. Steady-state measurements of daily Na⁺ excretion can indicate daily Na⁺ intake but cannot diagnose diuretic resistance (Figure 1). Presently, a practical and quantitative definition of diuretic resistance remains elusive.

Loop Diuretics and Dosage

Furosemide diuresis normally lasts about 4 hours. Bumetanide is somewhat shorter and torsemide somewhat longer. An approximate dose conversion ratio is 1:20:40:50 for bumetanide: torsemide: furosemide: ethacrynic acid. The normal ceiling daily dose of furosemide above which little further natriuresis occurs is 80 mg once or twice daily, increasing to 160 and 240 mg in patients with chronic kidney disease (CKD) stages 3 and 4 or nephrotic syndrome or 80 to 160 mg in patients with cirrhosis or HF with preserved GFR. Very high doses of circa 500 mg of furosemide may be required in patients with end-stage renal disease.⁶ The higher furosemide doses required for patients with CKD are a consequence of many factors including a decreased diuretic delivery to the kidney because of decreased renal blood flow (RBF), an increased volume of distribution of the protein-bound diuretic because of hypoalbuminemia, a decreased proximal tubule (PT) secretion of the diuretic by the organic anion transporters because of competition by urate and other organic anions that are retained in the plasma in patients with CKD, and a decreased filtered load of

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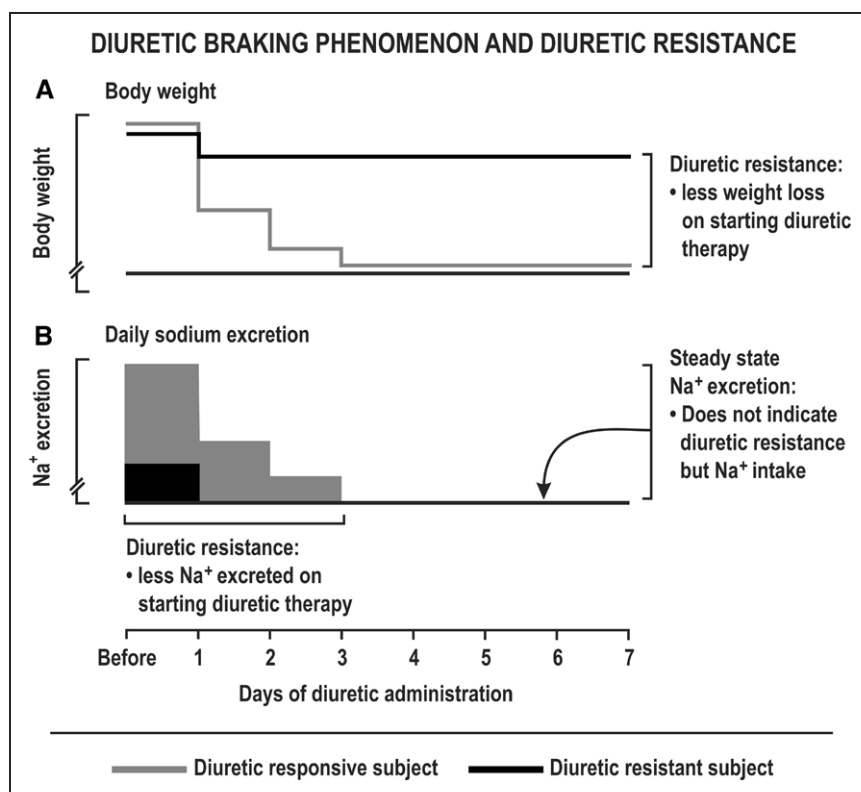


Figure 1. Diuretic braking phenomenon and diuretic resistance. Schematic representation of a diuretic responsive (gray lines and gray boxes) or resistant subject (dark lines and solid boxes), showing body weight (A) and daily sodium excretion (B) during loop diuretic administration.

Na⁺ because of a decreased GFR.⁷ However, the response to the diuretic delivered to the loop of Henle (LH) is well maintained in CKD. In practice, the dose of loop diuretics should generally be increased in proportion to the reduction in eGFR. Patients with CHF may have an impaired absorption of loop diuretics and an impaired tubular response mandating higher doses often given twice daily.⁸

Special problems with furosemide include a low and variable bioavailability of 10–80% that is impaired further in the elderly and those with HF or CKD.⁹ In theory, this should be addressed by intravenous dosing or by substituting torsemide or bumetanide that have higher and more consistent bioavailabilities.¹⁰ However, intravenous infusions are not strikingly superior to oral or bolus intravenous dosing (see later below) and variations in the gene expressions for the organic anion transporters and other genes adds to torsemide variability.^{11,12}

Individual Diuretic Responsiveness

The natriuretic response depends on salt intake,¹³ diuretic dose, renal function, and right atrial pressure.¹⁴ Whereas a low eGFR in patients with HF predicts a poor outcome, a worsening eGFR during hospitalization for acute HF in the Diuretic Optimization Strategies in Acute Heart Failure (DOSE) study paradoxically predicted a better outcome.¹⁵ This may reflect a successful hemodynamic response to renin-angiotensin-aldosterone system (RAAS) blockade that itself reduces the GFR but is beneficial for long term renal function.²

General Mechanisms of Diuretic Resistance and Tubular Responsiveness

Losses of body weight and Na⁺ are normally attenuated progressively during diuretic therapy (braking phenomenon; Figure 1). The initial 6-hourly natriuresis is enhanced

during high salt intake (Figure 2A), yet salt restriction is required to reduce Na⁺ balance (Figure 2B) or body weight (Figure 2C)¹³ because, during a high Na⁺ intake, the acute Na⁺ loss is restored by the kidneys after the diuresis by reduced Na⁺ excretion below intake, resulting in an unchanged Na⁺ balance (Figure 2D). However, during a low Na⁺ intake, even a very low level of postdiuretic Na⁺ excretion cannot restore Na⁺ balance because the acute natriuresis exceeds the dietary Na⁺ intake (Figure 2E). Thus, for diuretic-resistant patients, the daily Na⁺ intake should be less than the acute Na⁺ loss with the diuretic to ensure a negative Na⁺ balance. This value is 120 to 150 mmol in normal subjects but is reduced in those with CHF to about 50 to 100 mmol.¹⁶ However, whereas salt restriction increases diuretic-induced negative salt balance,¹³ it also increases renin, Ang II (angiotensin II), aldosterone, and renal K⁺ losses^{17,18} and may increase the risk of death in patients with HF.¹⁹ Restriction of daily Na⁺ intake to 80 to 120 mmol (2–3 g) is a reasonable target for patients with modest CHF and diuretic resistance.^{6,20}

After PT secretion, diuretics are confined to the tubular lumen. Thus, their rate of excretion approximates to their rate of delivery to their active site on the tubular lumen of the LH. A plot of increased Na⁺ excretion against diuretic excretion thereby provides an apparent dose-response relationship that approximates to tubular diuretic responsiveness.²¹ However, this relationship has marked hysteresis. Thus, the early points that fall on the ascent of the curve lead to much greater increases in Na⁺ excretion than the later points that fall on the descent of the curve. This finding implies the development of within-dose diuretic tolerance²² (Figure 3A). The initial few points on the steep part of the apparent dose-response curve represent highly efficient natriuresis but thereafter several

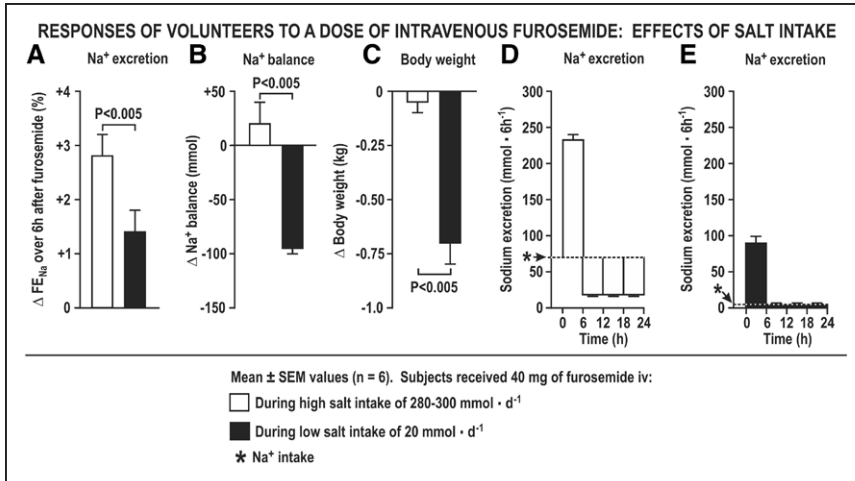


Figure 2. The effects of salt intake on the responses of volunteers to furosemide. Mean (\pm SEM) changes over 6 h (A) or over 24 h (B–E) after 40 mg of furosemide over 3 d during a daily sodium intake of 280 mmol (open boxes) or 20 mmol (closed boxes) depicting changes in fractional excretion of sodium for 6 h after the first dose of furosemide (A), daily sodium balance (B), changes in daily body weight over three days (C) and the patterns of 6-hourly sodium excretion (D and E).

points are effectively supramaximal, whereas later points fall on the truly inefficient descending curve (Figure 3B). Thus, a more prolonged delivery by an extended-release diuretic formulation can enhance diuretic efficiency.²²

Postdiuretic Sodium Retention

Although postdiuretic Na^+ retention follows a period of volume loss and activation of the RAAS and sympathetic nervous system,^{17,18,23} it is not normally modified by blockade of these systems.^{23,24} Indeed, 94% of an intravenous test load of 100 mmol NaCl given to volunteers was excreted over 2 days but, when given after bumetanide accompanied by an infusion of Na^+ , Cl^- , and fluid sufficient to prevent any volume depletion, only 9% was excreted.²⁵ Thus, postdiuretic renal Na^+ retention entails a memory effect of the pharmacological action of the diuretic on the renal tubules, rather than a response to volume loss.

Renal Hemodynamics

A reduction in the RBF limits the delivery of diuretic to the kidneys, whereas a reduction in the GFR limits the tubular Na^+ delivery. Thus, reductions in RBF or GFR can contribute to diuretic resistance.²⁶

Loop diuretics inhibit reabsorption by the tubular macula densa segment at the end of the LH that normally initiates afferent arteriolar vasoconstriction by the tubuloglomerular feedback response. Thus, tubuloglomerular feedback blockade

by loop diuretics should increase the RBF and GFR.²⁷ Indeed, furosemide increases the GFR in dogs.²⁸ However, it normally reduces the GFR and the RBF in rats,²⁹ mice,³⁰ and humans.³¹ The GFR falls by $\approx 23\%$ after furosemide^{13,18,23} or torsemide²² in normal subjects or those with HF.^{26,32} The fall in GFR in rats is independent of volume depletion or activation of the RAAS³³ but entails reflex renal vasoconstriction.^{33,34} Inhibition of tubular fluid reabsorption increases the tubular fluid volume³⁵ and this increases the intrarenal pressures since the kidney is encapsulated.^{36,37} This increase in renal turgor will directly restrict the RBF³⁸ but also will raise the renal interstitial pressure that activates the interstitial baroreceptors. In parallel, the diuretic will increase the urinary NaCl concentration that will activate the renal pelvic chemoreceptors. The ensuing increase in renal afferent nerve discharge should initiate a reno-renal reflex to increase renal efferent nerve activity and reduce the GFR and RBF³⁹ (Figure 4). Indeed, the fall in GFR with furosemide in rats is mitigated by renal nerve deafferentation.^{33,34} Renal afferent nerve activity is increased in rats with HF and enhances tubular Na^+ reabsorption, renin release, and renal vasoconstriction.⁴⁰ Although radiofrequency renal nerve ablation for patients with HF reduces parameters of volume overload and symptoms modestly,^{41–43} any effects on diuretic resistance have yet to be studied.

An aggressive diuresis in patients with diuretic-resistant CHF can increase the serum creatinine concentration. This is often ascribed to the concurrent use of RAAS inhibitors and

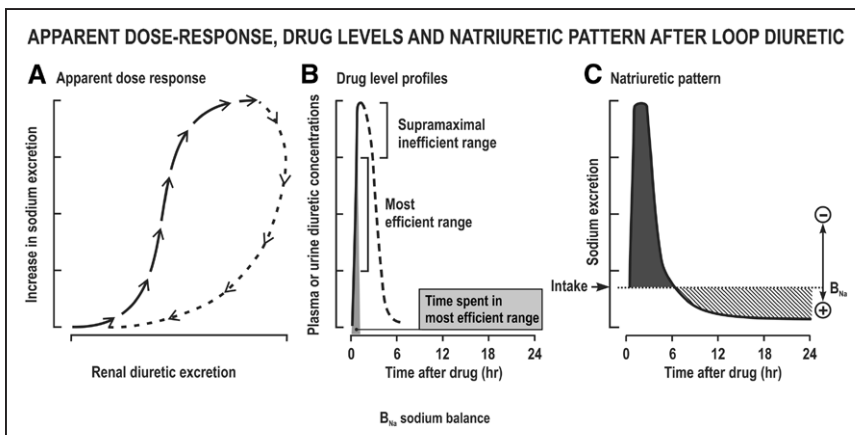


Figure 3. Apparent dose-response, diuretic plasma or urine levels, and natriuretic pattern after a loop diuretic. The apparent dose-response relationship at time points after a single dose (A), the profile of diuretics with the most efficient levels corresponding to the middle 50% of the rising phase (B) and the natriuretic pattern of brief sodium loss (negative balance) followed by Na^+ retention (positive balance; C).

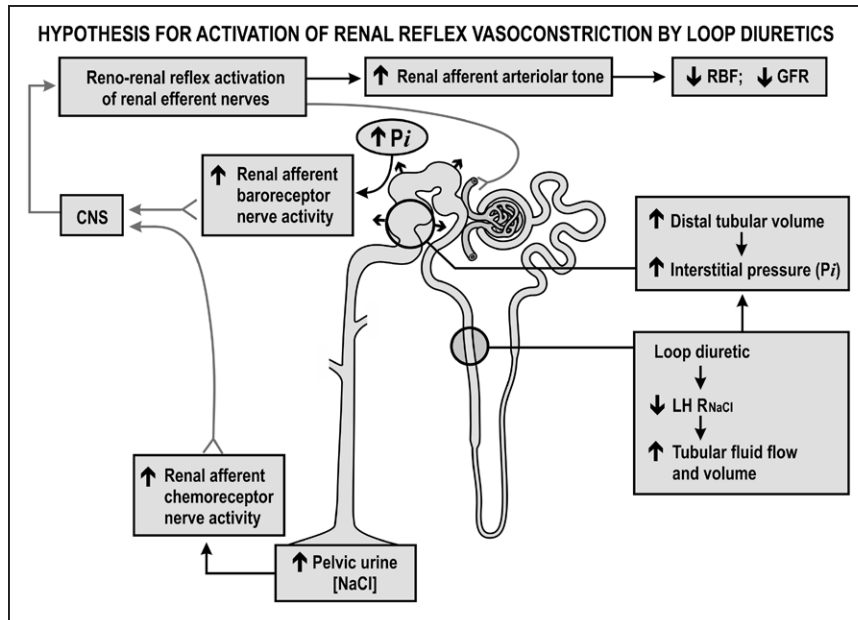


Figure 4. Hypothesis for activation of renal reflex vasoconstriction by loop diuretics. Diuretics reduce the reabsorption of sodium chloride in the loop of Henle (LH R_{NaCl}), distend the distal tubules, and increase the renal interstitial pressure (Pi) that activates renal afferent baroreceptor nerves but also increase the pelvic urine sodium chloride concentration that activates renal afferent chemoreceptor nerves. The increased afferent nerve discharge activates a central nervous system (CNS) reno-renal reflex that increases the renal efferent nerve activity and the afferent arteriolar tone that reduces the renal blood flow (RBF) and glomerular filtration rate (GFR).

taken as a sign of renal injury requiring a reduction in diuretic dosage or a change in therapy. However, whereas infusion of furosemide into euvoletic rats reduces their GFR and increases their renal vascular resistance, the concurrent administration of losartan does not modify the fall in GFR and reduces the renal vasoconstriction and filtration fraction.³³ Thus, a fall in GFR in this setting is not a manifestation of renal ischemia or damage. Moreover, an ACE (angiotensin-converting enzyme) inhibitor increases furosemide natriuresis modestly in normal subjects thereby reducing the work required for Na^+ reabsorption.⁴⁴ A study of patients with acute HF, most of whom were taking an RAAS inhibitor, reported that aggressive diuresis with an average daily intravenous dose of 150 mg of furosemide reduced the eGFR only modestly. Moreover worsening renal function was not associated with any increase in the excretion of markers of renal tubular injury. Indeed, an increase in the excretion of neutrophil gelatinase-associated lipocalin, N-acetyl- β -D-glucosaminidase, and kidney injury molecule 1 were associated paradoxically with improved 180-day patient survival.⁴⁵ These data indicate that the effects of a RAAS inhibitor on the renal hemodynamic response to a loop diuretic may entail some further reduction in GFR but likely a maintained or improved RBF and sometimes an increase in Na^+ excretion. The outcome of an improved RBF would be an improved renal O_2 delivery, whereas the outcome of a reduced GFR and increased Na^+ excretion would be a reduced renal O_2 usage because of a reduced workload by the tubules. This favorable O_2 balance should not induce renal ischemia or enhance renal tubular injury. Thus, the modest reduction in eGFR during intravenous loop diuretics during therapy with a RAAS inhibitor likely represents a favorable renal hemodynamic response rather than renal tubular injury and, therefore, should not normally be labeled acute kidney injury. It follows that a modest initial rise in serum creatinine concentration of <20% to 30% should not normally trigger withdrawal of the RAAS inhibitor therapy, but does require careful monitoring.

Hyponatremia and Hypokalemic, Hypochloremic, Metabolic Alkalosis

Loop diuretics and HF both provoke nonosmolar release of arginine vasopressin (AVP).⁴⁶ The increase in AVP in HF may enhance both V1aR (vasopressin type 1a receptor)-mediated vasoconstriction and V2R-mediated free water retention. Together, these may contribute to cardiac strain, worsening congestion, and hyponatremia.⁴⁷ The increase in plasma levels of AVP predicts bad outcomes in CHF,⁴⁸ whereas the increase in AVP with loop diuretics predicts poor diuresis, hyponatremia, and bad outcomes.⁴⁹ Tolvaptan blocks V2Rs and induces free water diuresis that corrects hyponatremia but can further increase AVP whose activation of V1aRs further enhances peripheral resistance and renal vasoconstriction.⁵⁰ Conivaptan blocks V2Rs and V1aRs and may, therefore, have a further benefit, but its interaction with diuretics requires study.⁵¹

Mild metabolic alkalosis reduces the natriuretic response to bumetanide by $\approx 20\%$, likely because of increased presentation of HCO_3^- , without Cl^- , to the NKCC2 (sodium, potassium, 2 chloride cotransporter) in the LH that has an absolute requirement for Cl^- for reabsorption with Na^+ and K^+ .⁵² Diuretic responses in hypochloremic patients are improved after correction of hypochloremia with lysine chloride.⁵³ Potassium depletion in rats halves the natriuretic response to furosemide.⁵⁴ Thus, hypokalemic, hypochloremic metabolic alkalosis should be corrected by concurrent use of a collecting duct (CD) diuretic (eg, amiloride or triamterene), a mineralocorticoid receptor antagonists (eg, spironolactone or eplerenone), or oral KCl.

Hypoalbuminemia, Albuminuria, and Albumin Infusion

Because loop diuretics are bound to albumen, hypoproteinemia increases their volume of distribution and reduces their renal delivery.⁵⁵ Mixing intravenous furosemide in a syringe with HSA (human serum albumin) improved urine output modestly in one study of patients with the nephrotic

syndrome.⁵⁵ However, furosemide should dissociate from circulating albumin in the circulation almost instantly, and these studies were not confirmed.⁵⁶ Proteinuria per se might impair the diuretic response by binding of the secreted diuretics to filtered albumin in tubular fluid. However, the coadministration of furosemide with sulfisoxazole that displaces bound furosemide did not modify the responses of proteinuric subjects to a loop diuretic.⁵⁷

Finally, infusions of salt poor HSA might increase the RBF and the delivery of the diuretic to the kidneys. However, an HSA infusion that increased the plasma volume by 23% actually reduced the Na^+ excretion and the GFR.⁵⁸ Moreover, although patients with the nephrotic syndrome infused with salt poor HSA had a modest increase in furosemide natriuresis, this was balanced by increased Na^+ intake from the salt poor albumin, resulting in unchanged Na^+ balance.⁵⁹ Infusion of albumin can cause hypertension, respiratory distress, HF,⁶⁰ and nephropathy.⁶¹ Thus, there is no clear place for albumin infusions to enhance diuretic responsiveness but rather these studies highlight many associated problems.

Diuretic Combinations

Diuretic therapy can upregulate Na^+ transport in the PT that limits Na^+ delivery to the LH or upregulates Na^+ transport in downstream nephron segments that limit natriuresis (Figure 5). These findings provide rationales for combining diuretics with actions on different nephron segments.

Loop Diuretic Plus PT Diuretic

Blockade of PT reabsorption by acetazolamide (Diamox) does not normally augment furosemide natriuresis^{62,63} likely because it increases the LH delivery of Na^+ with HCO_3^- , whereas reabsorption by the NKCC2 transporter in the LH is limited by Cl^- delivery.⁵² Although acetazolamide increased diuretic responsiveness in one experimental study, the authors related this to downregulation of $\text{Cl}^-/\text{HCO}_3^-$ exchange by pendrin in the CD.⁶⁴

SGLT2is (sodium-glucose linked transporter type 2 inhibitors) reduce PT reabsorption and synergize with loop diuretics to enhance natriuresis⁶⁵ as discussed.⁶⁶ Normal volunteers studied at a daily Na^+ intake of 110 mmol were randomized

to dapagliflozin or bumetanide for one week and crossed over. Natriuresis with bumetanide was increased significantly by 36% when tested after 1 week of dapagliflozin and natriuresis with dapagliflozin was increased significantly by 190% when tested after one week of bumetanide. The augmented loop diuretic response after adaptation to dapagliflozin likely occurred because the SGLT2i reduced PT reabsorption of Na^+ ⁶⁶ and thereby upregulated the downstream reabsorption of Na^+ in the LH that is the target for loop diuretics.⁶⁷ The augmented SGLT2i response after adaptation to bumetanide likely occurred because the loop diuretic released renin that generated Ang II that upregulated the expression of SGLT2 in the PT⁶⁸ that is the target for SGLT2i's. In another study, patients with CHF and type 2 diabetes mellitus were randomized for 2 weeks to empagliflozin versus placebo. Empagliflozin increased the Na^+ excretion with loop diuretics without enhancing the K^+ excretion⁶⁹ and reduced the plasma volume over 2 weeks. This occurred without activation of the RAAS or sympathetic nervous system and without a decline in the GFR or the appearance of tubular biomarkers of nephron damage.⁶⁹ Thus, SGLT2is may become important adjuncts to loop diuretic therapy for patients with CHF even in the absence of diabetes mellitus. Indeed, the recent Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial in patients with HF but without diabetes mellitus reported a significant reduction in CVD events and mortality in those randomized to dapagliflozin.⁷⁰ These results provide a rationale for the use of an SGLT2i to manage diuretic resistance in a wider range of patients with CHF, but this requires further evaluation.

Loop Diuretic Plus Early Distal Tubule Diuretic

Rats given furosemide develop massive hypertrophy of the distal tubule (DT),⁷¹ CD,⁷² and intercalated cells,⁷³ and a 3-fold increase in the Na^+ reabsorption by the DT.⁷⁴ Therefore, it is rational for patients resistant to loop diuretics to add a thiazide that blocks DT reabsorption.⁷⁵⁻⁷⁷ Frequently, metolazone is selected since it is available as an intravenous or oral preparation. Metolazone has a thiazide-like action and an additional effect to reduce PT reabsorption. An observational study reported that the use of metolazone with loop diuretics for patients with acute HF was associated with frequent electrolyte abnormalities and worsening renal function, whereas

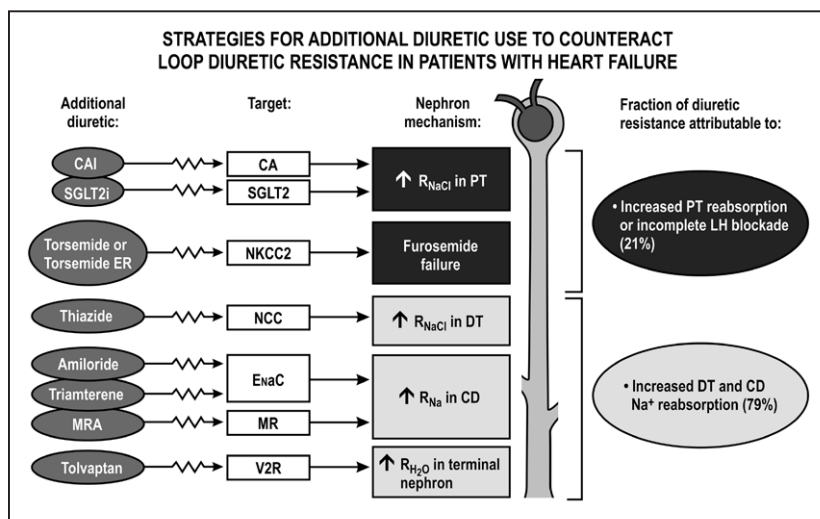


Figure 5. Strategies for the use of additional diuretics to counteract loop diuretic resistance in patients with heart failure. Schematic representation of nephron sites contributing to loop diuretic resistance and the major classes of diuretic drugs to correct these. Also shown is a summary from studies of patients with diuretic-resistant heart failure that apportioned the contribution to diuretic resistance between proximal effects that limited diuretic and sodium delivery to the loop of Henle (LH) and distal effects of increased reabsorption of sodium chloride (R_{NaCl}) in the distal tubule (DT) and collecting duct (CD). CA indicates carbonic anhydrase; CD, collecting duct; E_{Na}C, epithelial sodium channel; LH, loop of Henle; MR, mineralocorticosteroid receptor; MRA's, mineralocorticosteroid receptor antagonists; NCC, sodium, chloride cotransporter; NKCC2, sodium, potassium, 2 chloride transporter; PT, proximal tubule; R_{NaCl} , reabsorption of sodium chloride; SGLT2is, sodium-glucose linked transport 2 inhibitors; torsemide ER, torsemide extended-release; and V2R vasopressin type 2 receptor. Reprinted from Rao et al⁷⁵ with permission. Copyright ©2017.

high-dose furosemide therapy was associated with better outcomes.⁷⁸ Thus, up-titration of loop diuretics is a preferred initial step in the management of patients with diuretic-resistant acute HF. Although combined therapy with a loop diuretic and a thiazide can be helpful in patients with CHF⁷⁹ or edema,^{80,81} this strategy increases the frequency of hypokalemia, hypochloremia, hypomagnesemia, alkalosis, and azotemia and requires careful management. The benefits and complications of combined loop and thiazide diuretic therapy are illustrated in the clinical account of a patient with the nephrotic syndrome and resistance to 240 mg daily of furosemide (Figure 6). Dividing the daily furosemide dose in 2 had little effect. The addition of 80 mmol of KCl daily improved the hypokalemia modestly. However, the addition of only 25 mg of hydrochlorothiazide daily while maintaining the loop diuretic led to a 10 kg loss of body weight, but hypokalemia returned despite the large dose of oral KCl. The further addition of 100 mg of eplerenone daily to block the MR (mineralocorticosteroid receptor) restored normal serum potassium and led to a small further weight loss.

Loop Diuretic Plus CD Diuretic

Amiloride and triamterene block the epithelial sodium channel in the connecting tubule and CD. They can correct hypokalemic metabolic alkalosis since they secondarily inhibit the secretion of K⁺ and H⁺. Urine from proteinuric patients contains sufficient proteases such as plasmin to hydrolyze the luminal peptide loops of the epithelial sodium channel, thereby opening the Na⁺ channel and promoting Na⁺ reabsorption.^{82,83} This can be blocked by a CD diuretic. Indeed, CD diuretics enhance furosemide diuresis in children with minimal change glomerulonephritis,⁸⁴ patients with proteinuria and CHF,⁸⁵ and in other proteinuric conditions.⁸⁶ However, randomized clinical trials are presently lacking and CD diuretics can cause dangerous hyperkalemia.

Loop Diuretic Plus Mineralocorticoid Receptor Antagonists

The Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial reported that the addition of 100 mg of spironolactone daily to standard diuretic therapy for patients with worsening HF failed to improve outcomes.⁸⁷ This might be a consequence of prescribing spironolactone for only four days that may be insufficient to accumulate its active metabolite canrenone.

Loop Diuretics Plus PT and DT Diuretic, Mineralocorticosteroid Receptor Antagonists and Aquaretic

Diuretic resistance entails upregulation of the downstream Na⁺ transporters, thereby leading to impaired natriuresis on the one hand and to enhanced tubular K⁺ and H⁺ secretion in the distal nephron thereby leading to hypokalemic metabolic alkalosis on the other. This provides a rationale for segmental nephron blockade with multiple diuretic agents given concurrently to enhance diuretic responses but reduce electrolyte disturbances. Patients with acute HF and severe diuretic resistance treated with furosemide, metolazone, and spironolactone plus, in some, tolvaptan and acetazolamide and supplemental KCl had a daily loss of 3 to 4 L of fluid yet remarkably their serum electrolytes and creatinine were unchanged.⁸⁸ This novel strategy of segmental nephron blockade merits further prospective evaluation.

Dose Escalation or Intravenous Infusions of Loop Diuretics

Stepwise increases in the daily doses of intravenous furosemide from 125 to 250 to 500 mg failed to increase Na⁺ or fluid output of patients with refractory CHF.⁸⁹ Doubling the dose of

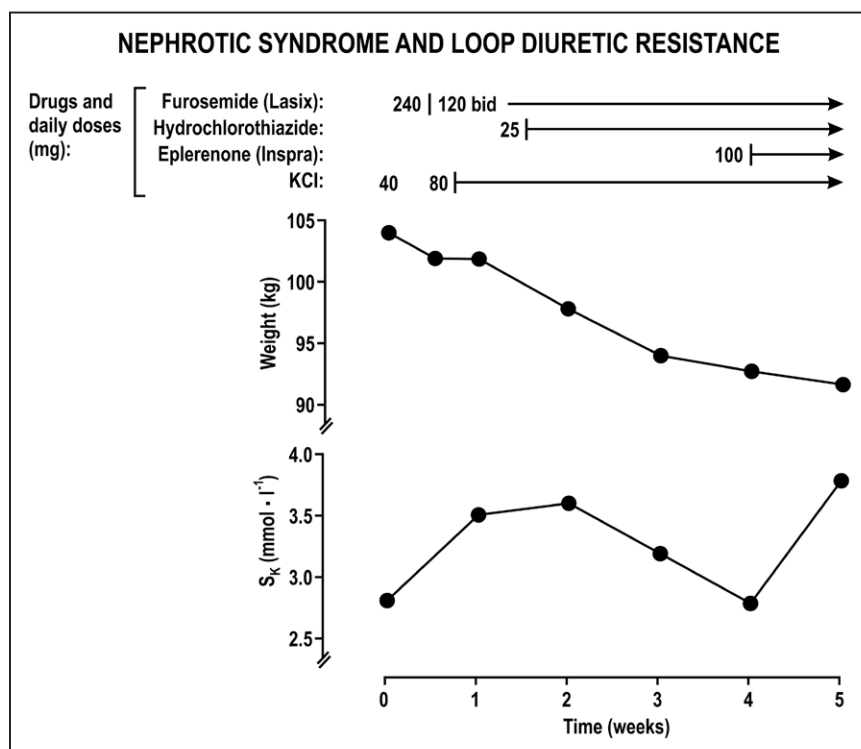


Figure 6. Response of a patient with furosemide-resistant edema from the nephrotic syndrome to treatment with diuretics and potassium chloride.

furosemide in the DOSE study did not affect the global assessment of symptoms in patients with severe HF.⁹⁰ However, in patients with less severe acute HF, each doubling of the dose of a loop diuretic increased daily Na⁺ excretion, albeit modestly, by 21 mmol.⁹¹ Thus, although dose escalation and twice-daily administration of loop diuretics is an appropriate initial therapy for most patients, increasing the daily dose above the ceiling does not usually relieve diuretic resistance. Many patients become resistant and require additional measures.^{6,20}

Another approach is to change from oral to intravenous loop diuretic administration. Infusions of furosemide, compared with intermittent doses, in patients with HF, increase urine output in some trials but the effects are generally modest,⁹² often unaccompanied by symptomatic improvement⁴

and unconfirmed in other trials.^{90,93,94} This may relate to the rapid development of tubular tolerance²² (Figure 3A).

Long-Acting Formulations

Recently, 20 mg of an extended-release formulation of torsemide, compared with 20 mg of an immediate-release formulation, was reported to double the Na⁺ and fluid losses without increasing K⁺ excretion.²² This was related to a longer time on the efficient ascending phase of the natriuresis/torsemide excretion relationship (Figure 3A), a limited time for postdiuretic Na⁺ retention (Figure 3C) and a better maintained GFR. Torsemide extended-release produced a negative Na⁺ balance in subjects receiving ≈300 mmol of Na⁺ daily that, if confirmed, might lessen the need for restriction of salt intake.

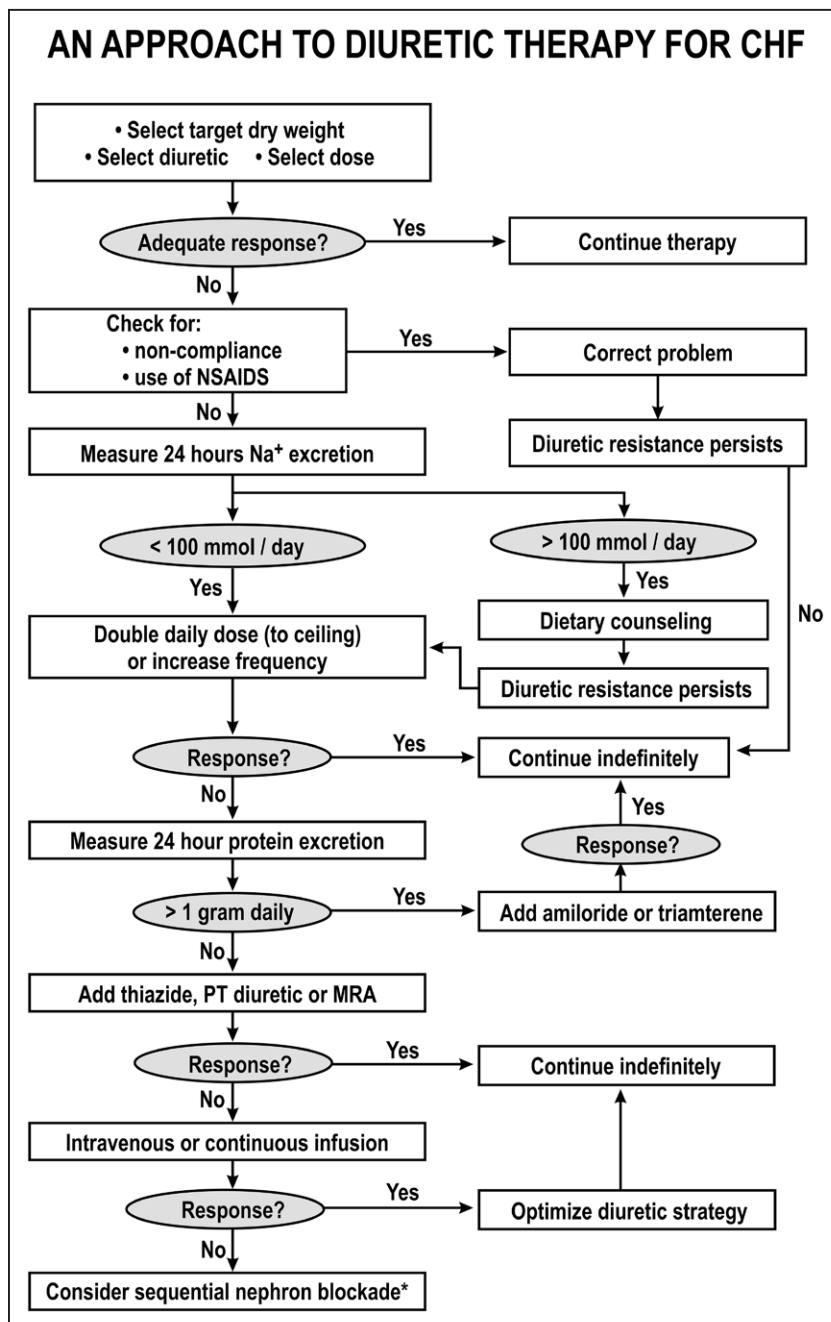


Figure 7. Diagrammatic representation of an approach to the management of diuretic resistance in patients with heart failure. MRA indicates mineralocorticosteroid antagonist; NSAIDs, nonsteroidal anti-inflammatory agents; and PT, proximal tubule. *Experimental therapy.

Perspectives

Resistance to diuretics is a frequent, but a sometimes preventable or reversible, cause of hospitalization for congestion, and worsening symptoms. Unfortunately, clinical signs and symptoms are often unreliable to detect diuretic resistance. The development of new diuretics, strategies, or combinations is important to overcome diuretic resistance. Many factors can contribute to diuretic resistance that provide rationales for the use of specific interventions. As recently presented,⁶ these strategies are shown in Figure 7. However, they have not been rigorously tested in clinical trials. Therefore, this should be used as a guide for consideration of appropriate treatment rather than a rigorous algorithm.

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