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# THE 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 (GFR) or heart failure (HF)]. It is a major cause of recurrent hospitalizations in patients with chronic heart failure (CHF) 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.

### Keywords

Furosemide; torsemide; edema; diuretic combinations

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## Introduction definition and clinical impact:

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 – 2 hours after a loop diuretic can be used to predicts $Na^+$ output. An $Na^+$ 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 patients [2]:

$Na^+$ output (mmol) = eGFR (BSA/1.73) ($S_{Cr}/U_{Cr}$) * 60 min * 2.5 hr * ($U_{Na}$/1000 ml) where BSA is body surface area, 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 – 160 mg in patients with cirrhosis or HF with preserved glomerular filtration rate (GFR). Very high doses of circa 500 mg of furosemide may be required in patients with end stage renal disease (ESRD) [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 secretion of the diuretic by the organic anion transporters (OATs) 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 $Na^+$ because of a decreased GFR [7]. However, the response to the diuretic delivered to the loop of Henle 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 iv dosing or by substituting torsemide or bumetanide that have higher and more consistent bioavailabilities [10]. However, iv infusions are not strikingly superior to oral or bolus iv dosing (see later below) and variations in the gene expressions for the OATs 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 heart failure (AHF) in the 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 post-diuretic $Na^+$ 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 – 150 mmol in normal subjects but is reduced in those with CHF to about 50 – 100 mmol [16]. However, whereas salt restriction increases diuretic-induced negative salt balance [13], it also increases renin, angiotensin II (Ang 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 80–120 mmol (2 – 3 grams) is a reasonable target for patients with modest CHF and diuretic resistance [6, 20].

After proximal tubule (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 loop of Henle (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 tolerance [22] (Figure 3A). The initial few points on the steep part of the apparent “dose response curve” represent highly efficient natriuresis but

thereafter several points are effectively “supra-maximal”, while 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].

## Post diuretic sodium retention:

Although post-diuretic $Na^+$ retention follows a period of volume loss and activation of the RAAS and sympathetic nervous system (SNS) [17, 18, 23], it is not normally modified by blockade of the RAAS or the SNS [23, 24]. Indeed, 94% of an iv test load of 100 mmol NaCl given to volunteers was excreted over two 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, post diuretic 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 while 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 (TGF) response. Thus TGF 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 ~23% after furosemide [13, 18, 23] or torsemide [22] in normal subjects or those with HF [26, 32]. The fall in GFR in rats is independent of volume depletion or activation of the RAAS [33] but entails reflex renal vasoconstriction [33, 34]. Inhibition of tubular fluid reabsorption increases the tubular fluid volume [35] and this increases the intrarenal pressures since the kidney is encapsulated [36, 37]. This increase in renal turgor will directly restrict the RBF [38] but also will raise the renal interstitial pressure (Pi) 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 RBF [39] (Figure 4). Indeed, the fall in GFR with furosemide in rats is mitigated by renal nerve deafferentation [34, 40]. Renal afferent nerve activity is increased in rats with HF and enhances tubular $Na^+$ reabsorption, renin release and renal vasoconstriction [41]. While radiofrequency renal nerve ablation for patients with HF reduces parameters of volume overload and symptoms modestly [42–44], 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 (Scr). This is often ascribed to the concurrent use of RASS inhibitors and taken as a sign of renal injury requiring a reduction in diuretic dosage or a change in therapy. However, whereas infusion of furosemide into euvolemic 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 angiotensin converting enzyme inhibitor (ACEI) increases furosemide natriuresis modestly in normal subjects thereby reducing the work required for $Na^+$ reabsorption [45]. A study of patients with acute heart failure, most of whom were taking an RASS 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 an improved 180-day patient survival [46]. These data indicate that the effects of an RASS 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 while the outcome of a reduced GFR and increased $Na^+$ excretion would be a reduced renal $O_2$ usage because of a reduced work load 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 an RASS 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 Scr of < 20 – 30% should not normally trigger withdrawal of the RASS inhibitor therapy, but does require careful monitoring.

## Hyponatremia and hypokalemic, hypochloremic, metabolic alkalosis:

Loop diuretics and heart failure both provoke non-osmolar release of arginine vasopressin (AVP) [47]. The increase in AVP in HF may enhance both vasopressin type 1a receptor (V1aR)-mediated vasoconstriction and V2R-mediated free water retention. Together, these may contribute to cardiac strain, worsening congestion and hyponatremia [48]. The increase in plasma levels of AVP predict bad outcomes in CHF [49] while the increase in AVP with loop diuretics predicts poor diuresis, hyponatremia and bad outcomes [50]. Tolvaptan blocks V2Rs and induces free water diuresis that corrects hyponatremia, but can further increase AVP whose activation of VIaRs further enhances peripheral resistance and renal vasoconstriction [51]. Conivaptan blocks V2Rs and V1aRs and may therefore have a further benefit, but its interaction with diuretics requires study [52].

Mild metabolic alkalosis reduces the natriuretic response to bumetanide by ~20%, likely because of increased presentation of $HCO_3^-$, without $Cl^-$, to the sodium, potassium, 2 chloride (NKCC2) co-transporter in the LH that has an absolute requirement for $Cl^-$ for reabsorption with $Na^+$ and $K^+$ [53]. Diuretic responses in hypochloremic patients are improved after correction of hypochloremia with lysine chloride [54]. Potassium depletion in rats halves the natriuretic response to furosemide [55]. Thus hypokalemic, hypochloremic metabolic alkalosis should be corrected by concurrent use of a collecting duct (CD) diuretic (e.g. amiloride or triamterene), a mineralocorticosteroid receptor antagonists (MRA; e.g. spironolactone or eplerenone) or oral KCl.

## Hypoalbuminemia, albuminuria and albumin infusion:

Since loop diuretics are bound to albumen, hypoproteinemia increases their volume of distribution and reduces their renal delivery [56]. Mixing iv furosemide in a syringe with human serum albumin (HSA) improved urine output modestly in one study of patients with the nephrotic syndrome [56]. However, furosemide should dissociate from circulating albumin in the circulation almost instantly and these studies were not confirmed [57]. Proteinuria *per se* might impair the diuretic response by binding of the secreted diuretics to filtered albumin in tubular fluid. However, the co-administration of furosemide with sulfisoxazole that displaces bound furosemide did not modify the responses of proteinuric subjects to a loop diuretic [58].

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 [59]. 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 [60]. Infusion of albumin can cause hypertension, respiratory distress, HF [61] and nephropathy [62]. 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 limits natriuresis (Figure 5). These findings provide rationales for combining diuretics with actions on different nephron segments.

## Loop diuretic plus proximal tubule (PT) diuretic:

Blockade of PT reabsorption by acetazolamide (Diamox) does not normally augment furosemide natriuresis [63, 64] likely because it increases the LH delivery of $Na^+$ with $HCO_3^-$, whereas reabsorption by the NKCC2 transporter in the loop of Henle is limited by $Cl^-$ delivery [53]. Although acetazolamide increased diuretic responsiveness in one experimental study, the authors related this to downregulation of $Cl^-/HCO_3^-$ exchange by pendrin in the CD [65].

Sodium glucose linked transporter type 2 inhibitors (SGLT2i's) reduce PT reabsorption and synergize with loop diuretics to enhance natriuresis [66] as discussed [67]. Normal volunteers studied at a daily $Na^+$ intake of 110 mmol were randomized to dapagliflozen or bumetanide for one week and crossed over. Natriuresis with bumetanide was increased significantly by 36% when tested after one 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 $Na^+$ [67] and thereby upregulated the downstream reabsorption of $Na^+$ in the loop of Henle that is the target for loop diuretics [68]. 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 PT [69] that is

the target for SGLT2i's. In another study, patients with CHF and type 2 diabetes mellitus were randomized for two weeks to empagliflozin vs placebo. Empagliflozin increased the $Na^+$ excretion with loop diuretics without enhancing the $K^+$ excretion [70] and reduced the plasma volume over two weeks. This occurred without activation of the RAAS or SNS and without a decline in the GFR or the appearance of tubular biomarkers of nephron damage [70]. Thus, SGLT2i's may become important adjuncts to loop diuretic therapy for patient with CHF even in the absence of diabetes mellitus. Indeed, the recent 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 [71]. 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 (DT) diuretic:

Rats given furosemide develop massive hypertrophy of the DT [72], CD [73], and intercalated cells [74] and a 3-fold increase in the $Na^+$ reabsorption by the distal tubule [75]. Therefore, it is rational for patients resistant to loop diuretics to add a thiazide that blocks DT reabsorption [76–78]. 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 AHF was associated with frequent electrolyte abnormalities and worsening renal function whereas high-dose furosemide therapy was associated with better outcomes [79]. Thus, uptitration of loop diuretics is a preferred initial step in the management of patients with diuretic resistant AHF. Although combined therapy with a loop diuretic and a thiazide can be helpful in patients with CHF [80] or edema [81, 82], 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 two 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 mineralocoricostroid receptor (MR) restored a normal serum potassium and led to a small further weight loss.

## Loop diuretic plus collecting duct (CD) diuretic:

Amiloride and triamterene block the epithelial sodium channel ($E_{Na}C$) 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 $E_{Na}C$ thereby opening the $Na^+$ channel and promoting $Na^+$ reabsorption [83, 84]. This can be blocked by a CD diuretic. Indeed, CD diuretics enhance furosemide diuresis in children with minimal change glomerulonephritis [85], patients with proteinuria and CHF [86] and in other proteinuric

conditions [87]. However, randomized clinical trials are presently lacking and CD diuretics can cause dangerous hyperkalemia.

## Loop diuretic plus mineralocorticoid receptor antagonists (MRAs):

The 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 [88]. 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, MRA 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 – 4 l of fluid yet remarkably their serum electrolytes and creatinine were unchanged [89]. 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 iv furosemide from 125 to 250 to 500 mg failed to increase $Na^+$ or fluid output of patients with refractory CHF [90]. Doubling the dose of furosemide in the DOSE study did not affect the global assessment of symptoms in patients with severe HF [91]. However, in patients with less severe AHF, each doubling of the dose of a loop diuretic increased daily $Na^+$ excretion, albeit modestly, by 21 mmol [92]. Thus, while 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 iv loop diuretic administration. Infusions of furosemide, compared to intermittent doses, in patients with HF increase urine output in some trials but the effects are generally modest [93], often unaccompanied by symptomatic improvement [4] and unconfirmed in other trials [91, 94, 95]. This may relate to the rapid development of tubular tolerance [22] (Figure 3A).

## Long acting formulations:

Recently, 20 mg of an extended release (ER) formulation of torsemide, compared to 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 post-diuretic $Na^+$ retention (Figure 3C) and a better maintained GFR. Torsemide

ER 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.

## 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 are 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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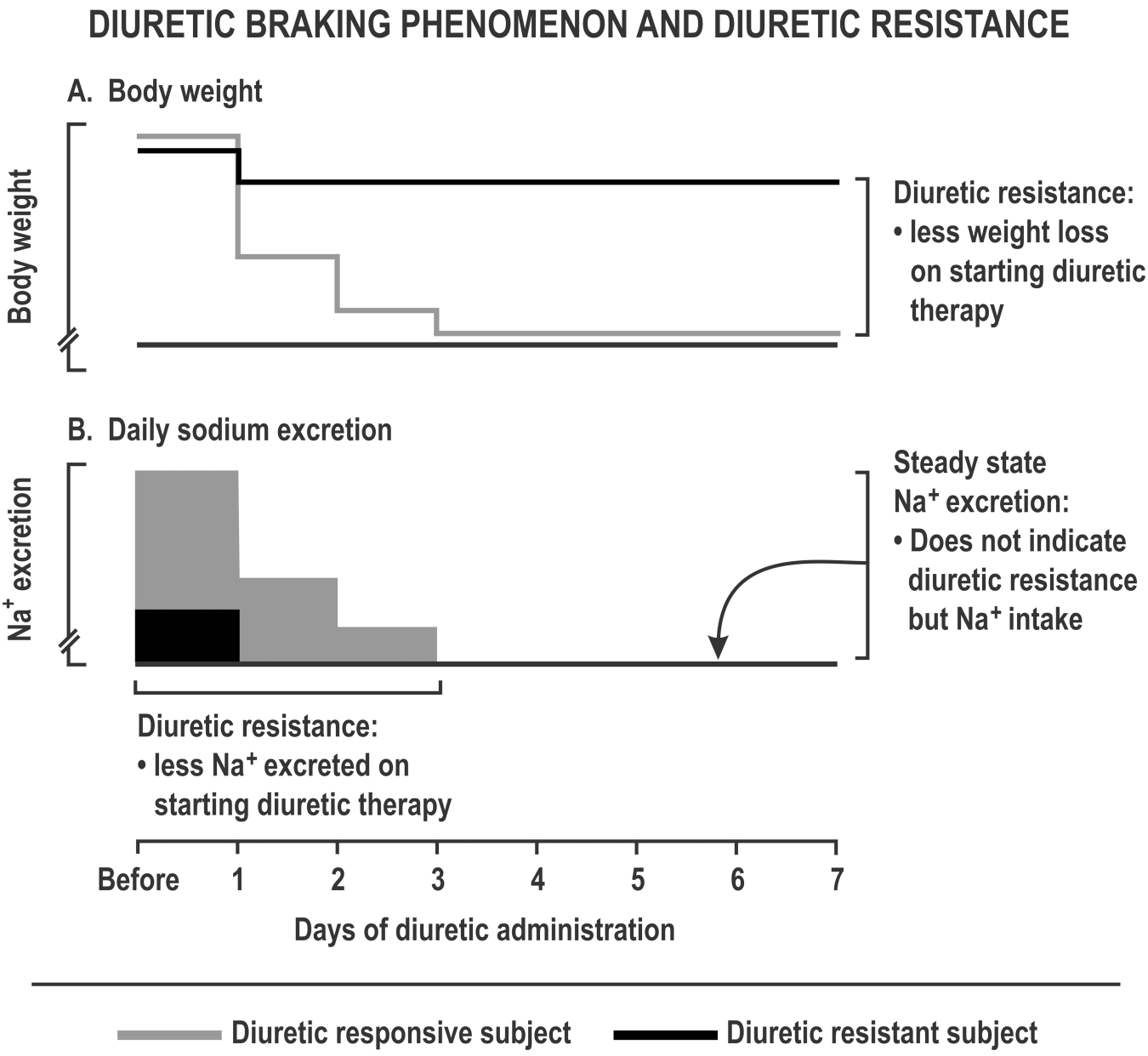


**Figure 1. Diuretic braking phenomenon and diuretic resistance:**

Schematic representation of a diuretic responsive (grey lines and grey boxes) or resistant subject (dark lines and solid boxes), showing body weight (Panel A) and daily sodium excretion (Panel B) during loop diuretic administration.

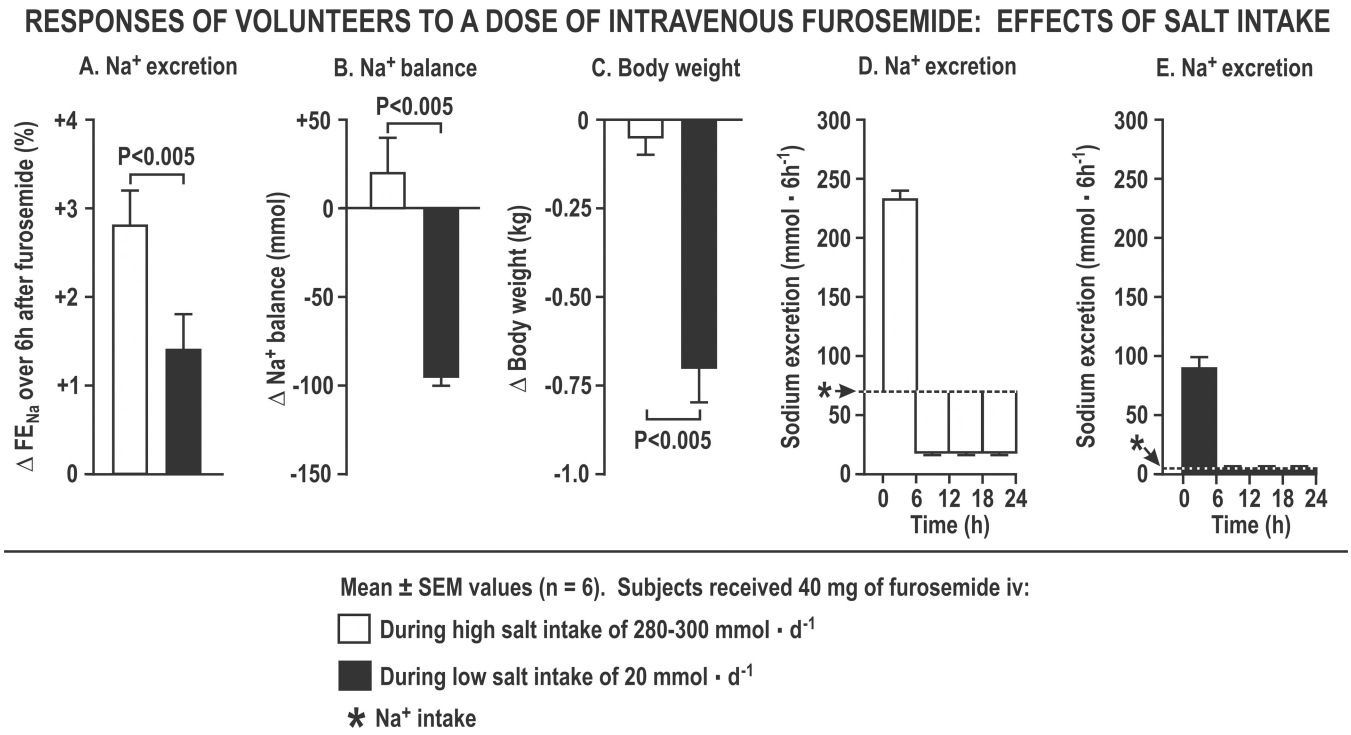


**Figure 2. The effects of salt intake on the responses of volunteers to furosemide:**

Mean (± sem) changes over 6 hours (Panel A) or over 24 hours (Panels B to E) after 40 mg of furosemide over three days during a daily sodium intake of 280 mmol (open boxes) or 20 mmol (closed boxes) depicting changes in fractional excretion of sodium for 6 hours after the first dose of furosemide (Panel A), daily sodium balance (Panel B), changes in daily body weight over three days (Panel C) and the patterns of 6 hourly sodium excretion (Panels D and E).

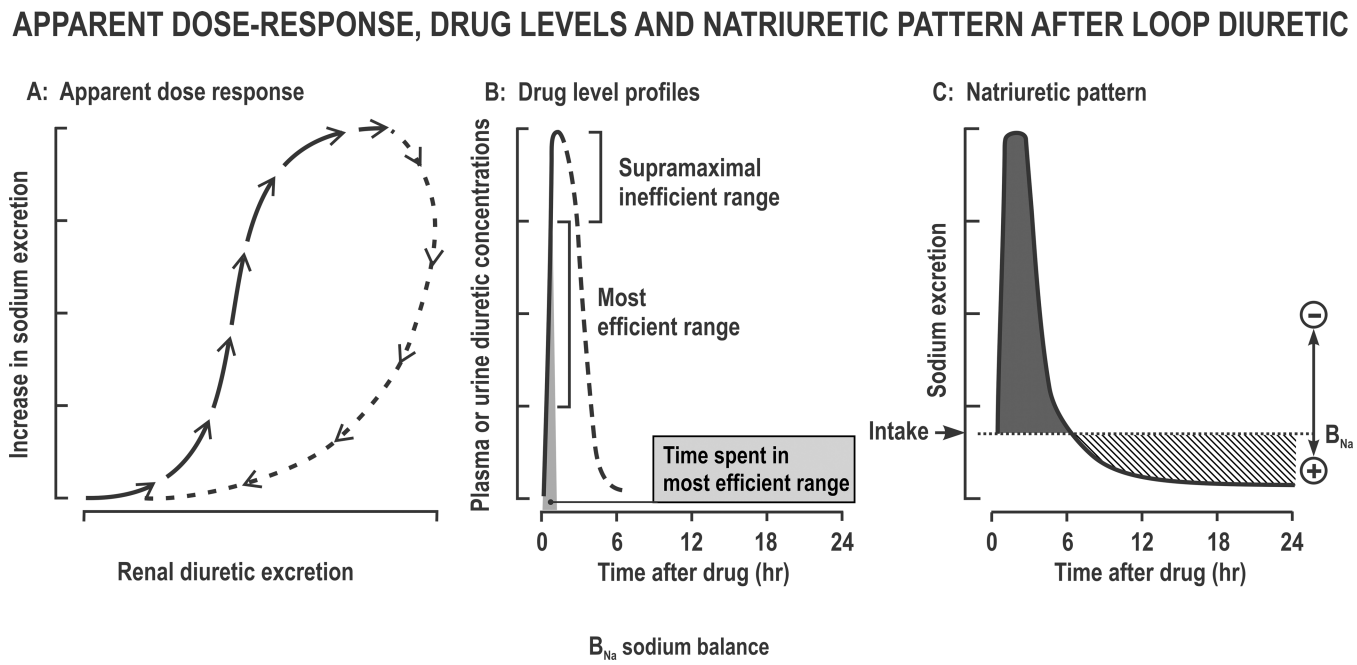


**Figure 3. Apparent Dose-Response, diuretic plasma or urine levels and natriuretic pattern after a loop diuretic:**

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

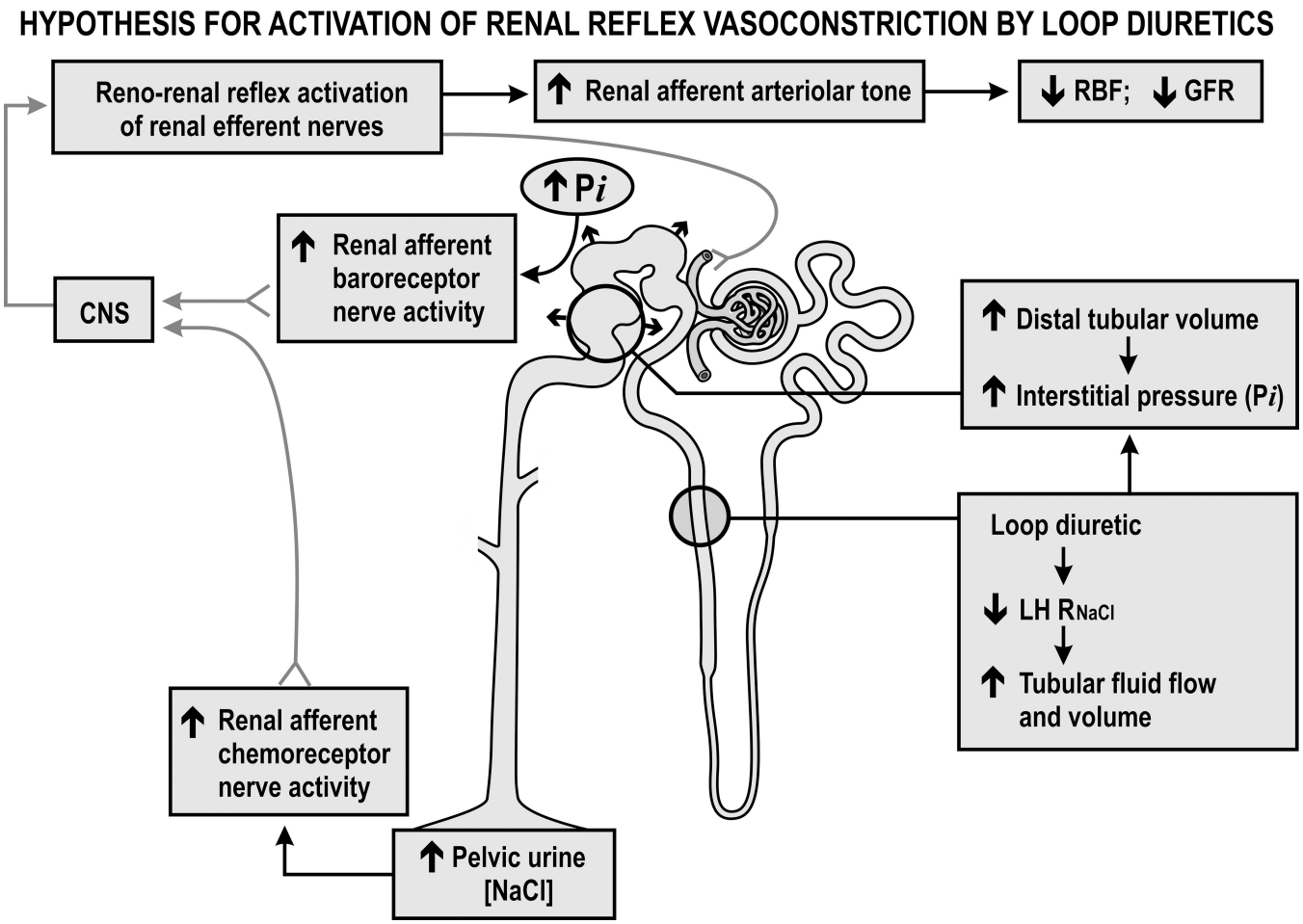


**Figure 4. Hypothesis for activation of renal reflex vasoconstriction by loop diuretics:**

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 and glomerular filtration rate.

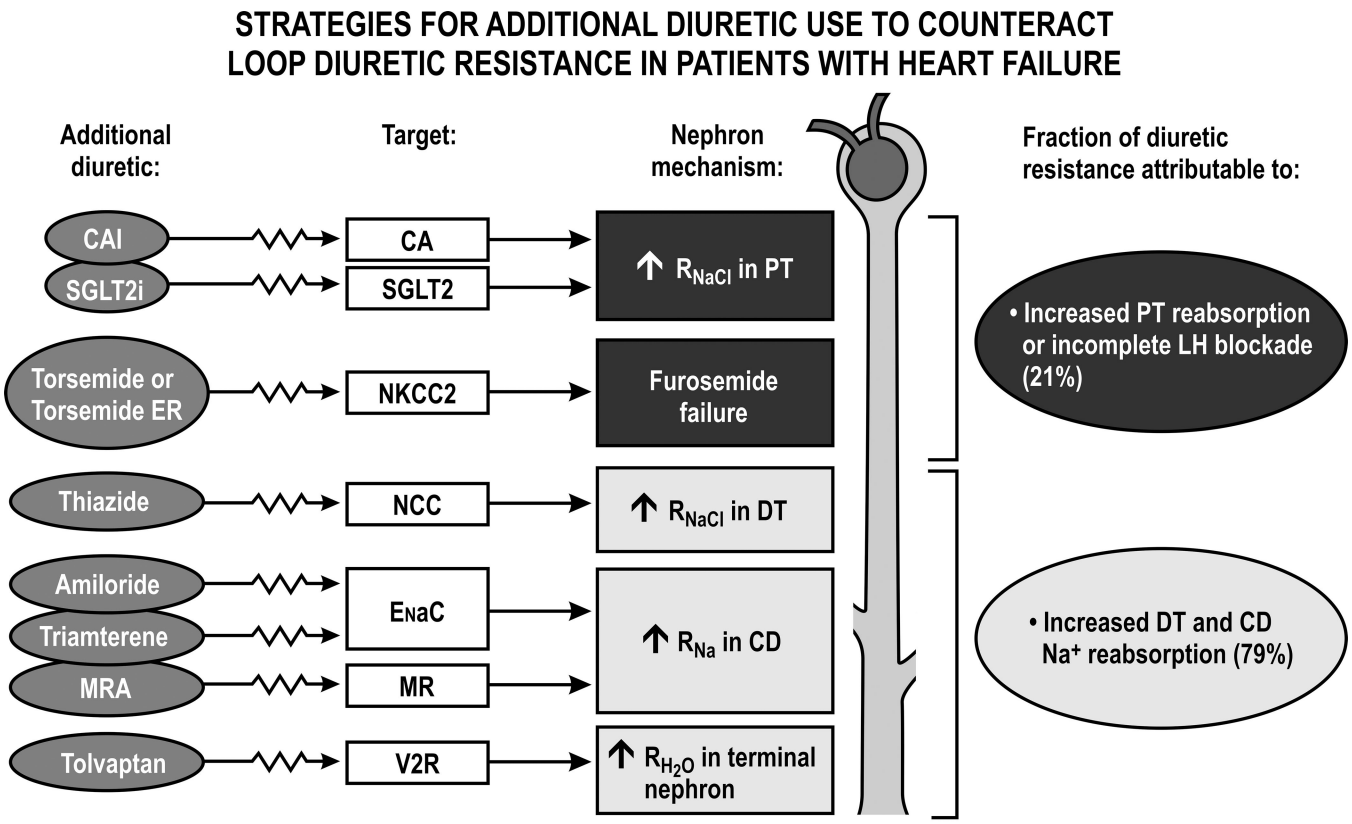


**Figure 5. Strategies for the use of additional diuretics to counteract loop diuretic resistance in patients with heart failure:**

Schematic representation of nephron sites contributing to loop diuretic resistance and the major classes of diuretic drug to correct these. CAIs, carbonic anhydrase inhibitors; CA, carbonic anhydrase; SGLT2i's, sodium glucose linked transport 2 inhibitors; torsemide ER, torsemide extended release; NKCC2, sodium, potassium, 2 chloride transporter; NCC, sodium, chloride cotransporter; $E_{Na}C$, epithelial sodium channel; V2 vasopressin type 2 receptor; MRA's, mineralocorticosteroid receptor antagonists; $R_{NaCl}$, reabsorption of sodium chloride; PT, proximal tubule; LH, Loop of Henle; DT, distal tubule; CD, collecting duct. 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 LH and distal effects of increased $R_{NaCl}$ in the DT and CD. After Rao, V et al, J Am Soc Nephrol 28:3414–3424, 2017, with permission.

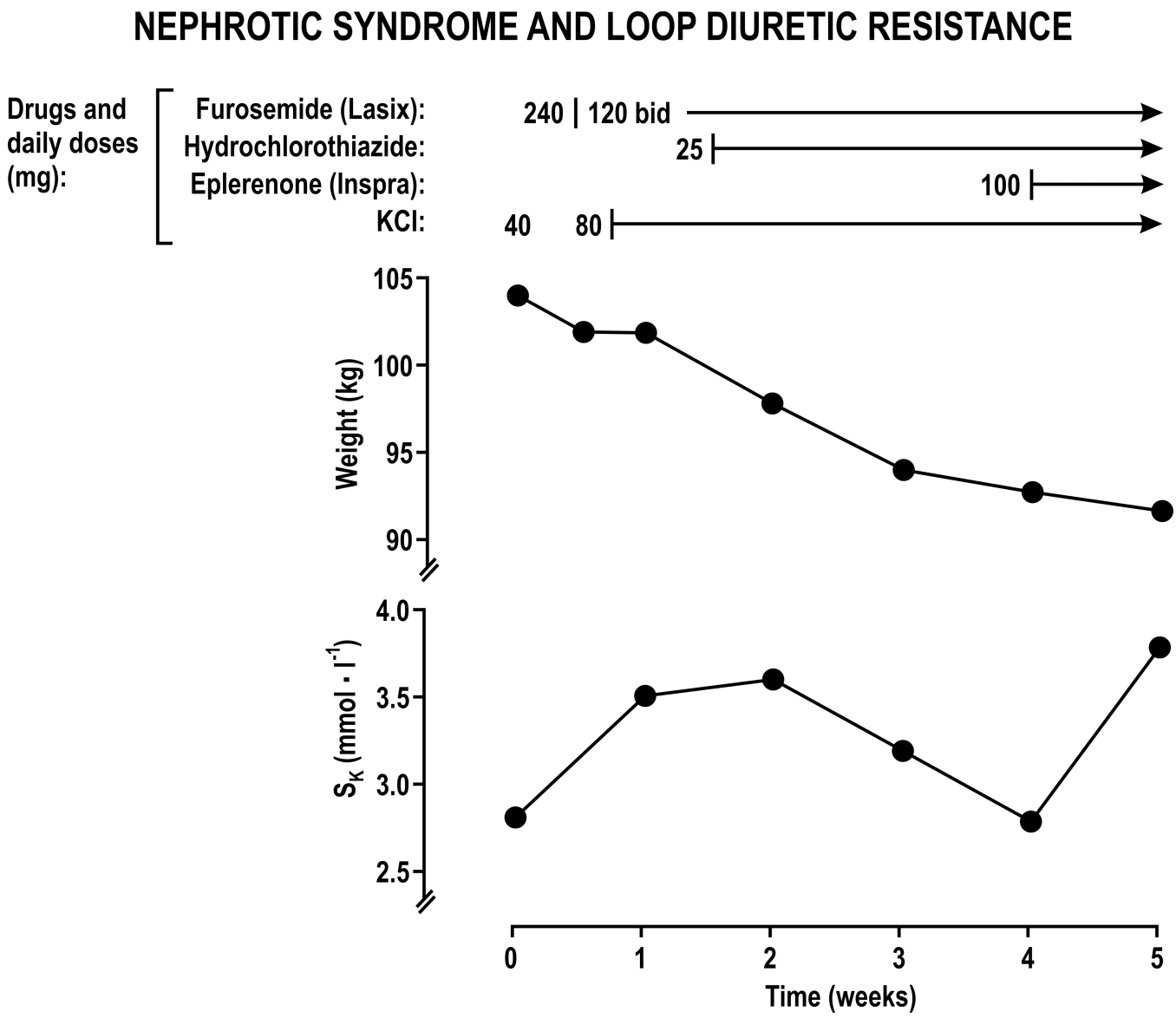


**Figure 6. Response of a patient with furosemide-resistant edema from the nephrotic syndrome to treatment with diuretics and potassium chloride.**

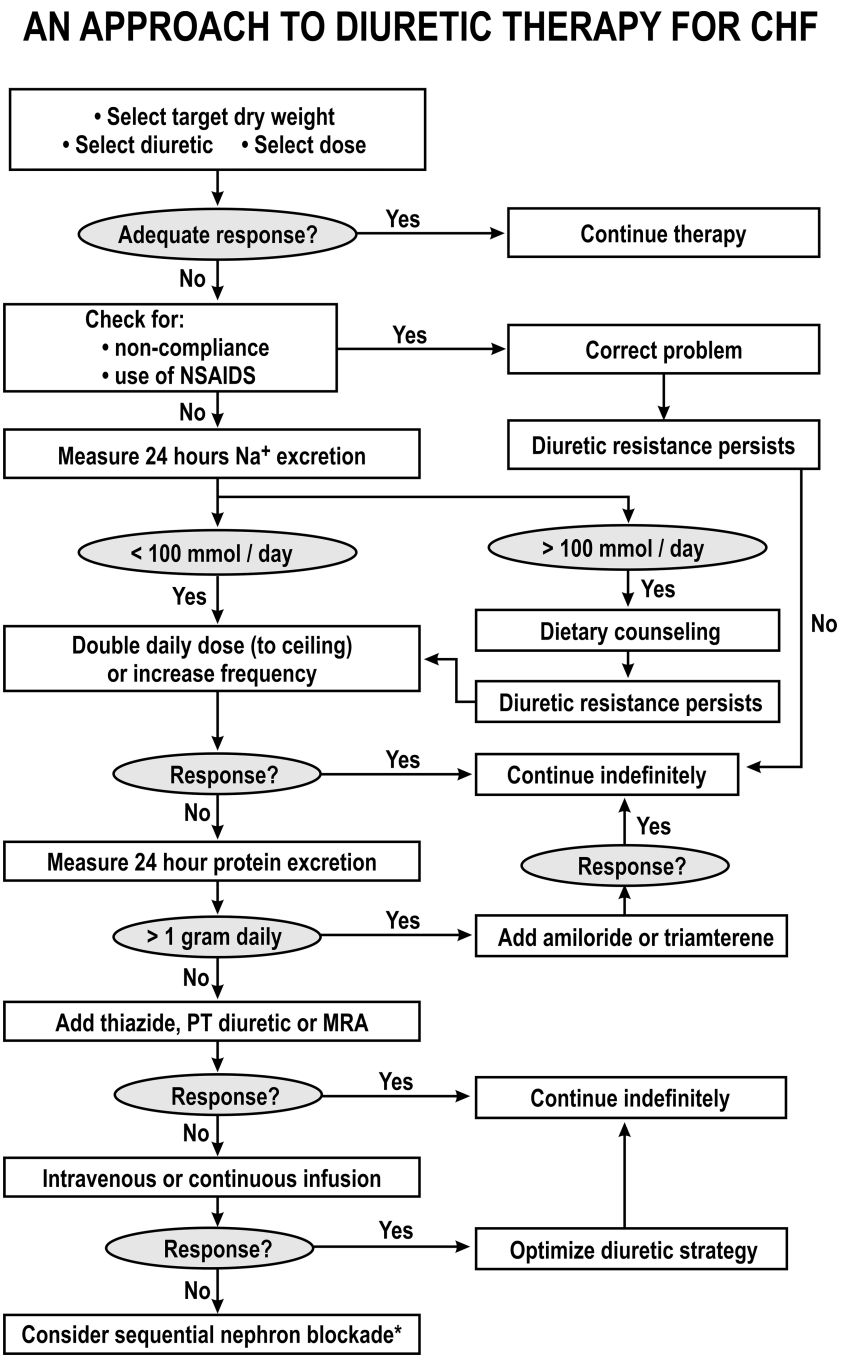


**Figure 7. Diagrammatic representation of an approach to the management of diuretic resistance in patients with heart failure:**

DCT, distal convoluted tubule diuretic; NSAIDs, non-steroidal anti-inflammatory agents; PT, proximal tubule; MRA, mineralocorticosteroid antagonist *, experimental therapy.