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Management of congestion and diuretic resistance in heart failure

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ABSTRACT

We present the case of a patient with heart failure and severe congestion who was responding poorly to diuretic therapy. We discuss the key problems concerning the pathophysiology and bedside therapeutic approach to congestion and fluid overload in this clinical setting, and we give practical suggestions to overcome congestion, especially in the setting of diuretic resistance and worsening renal function. We conclude that the application of key pharmacokinetic and pharmacodynamic principles of diuretic therapy, along with in-depth knowledge of the pathophysiology of heart failure, still represent the cornerstones for a correct approach to decongestive therapy in these patients.

Keywords: Congestion, Diuretic resistance, Heart failure

Case report

A 76-year-old male patient with coronary artery disease (CAD), who had undergone coronary artery bypass grafting (CABG) 4 years before the present evaluation, had left ventricle dilatation and severe systolic dysfunction (ejection fraction [EF] 30%), and was regularly being followed at an outpatient heart failure (HF) clinic. He had type 2 diabetes mellitus and was undergoing treatment with repaglinide. He had undergone a coronary artery angiography 3 months earlier; no interventional procedures had been performed, nor had any indications for heart surgery been established. His usual serum creatinine (sCr) value was 1.8 mg/dL (estimated glomerular filtration rate [eGFR] by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula was 37 mL/min per 1.73 m^2). His usual weight was 80 kg, and his height was 172 cm. In the last 6 months he had been repeatedly admitted (3 times) to cardiology or internal medicine units for worsening dyspnea and weight gain. His usual therapy included ramipril 5 mg once daily (o.d.), bisoprolol 2.5 mg twice daily (b.i.d.), acetylsalicylic acid (ASA) 100 mg o.d., atorvastatin 20 mg o.d., spironolactone 25 mg o.d. and oral furosemide 50 mg o.d., which had been increased to 125 mg every 48 hours in the last week. The patients was sent to the emergency department by his general practitioner for "refractory heart failure." The patient was subsequently admitted to an internal medicine ward. At admission he was dyspneic, his peripheral O_2 saturation was 93% in air, and he had bilateral pitting leg edema. Chest X-ray showed interstitial edema and a small bilateral pleural effusion. His blood pressure was 125/80 mm Hg, and his pulse rate was 70 bpm and rhythmic. His weight was 87 kg (+7 kg vs. usual weight). Laboratory data were as follows: sCr 2.1 mg/dL, blood urea nitrogen (BUN) 51 mg/dL, Na 133 mmol/L, K 4.7 mmol/L and plasma HCO_3^- 32 mmol/L. Diuretic treatment was changed to furosemide 125 mg in single intravenous (i.v.) bolus and canrenoate 100 mg i.v. o.d. Three days later, sCr had increased to 2.7 mg/dL, BUN was 95 mg/dL and Na 128 mmol/L. Dyspnea and dependent edema were still present, and 24-hour urinary volume was approximately 1,700 mL. Due to the sCr increase and hyponatremia, diuretic treatment was stopped. A nephrologist was consulted for possible ultrafiltration.

At the time of the renal consultation, the patient's weight was 88 kg (+1 kg vs. at admission). He was started on fluid restriction (≤750 mL/day) and a low-sodium diet + NaCl intake 2 g/day. A fractionated 24-hour urine collection was obtained while the patient was still on the previous treatment: 1,350 mL were collected in the first 12 hours after diuretic administration, and 450 mL in the following 12 hours. Furosemide administration was initially changed to 60 mg i.v., every 8 hours, then shifted to 125 mg b.i.d. per os (p.o.). Potassium canrenoate 100 mg i.v. o.d. was maintained. A diuretic treatment regimen was implemented with metolazone 5 mg b.i.d. p.o. and acetazolamide 250 mg b.i.d. p.o.; potassium chloride supplements (16 mEq three times a day [t.i.d.] p.o.) were added. A week later, a cumulative 10 kg weight loss had been obtained; sCr was 2.0 mg/dL, BUN 60 mg/dL, serum Na 136 mmol/L and plasma HCO_3^- 28 mmol/L.

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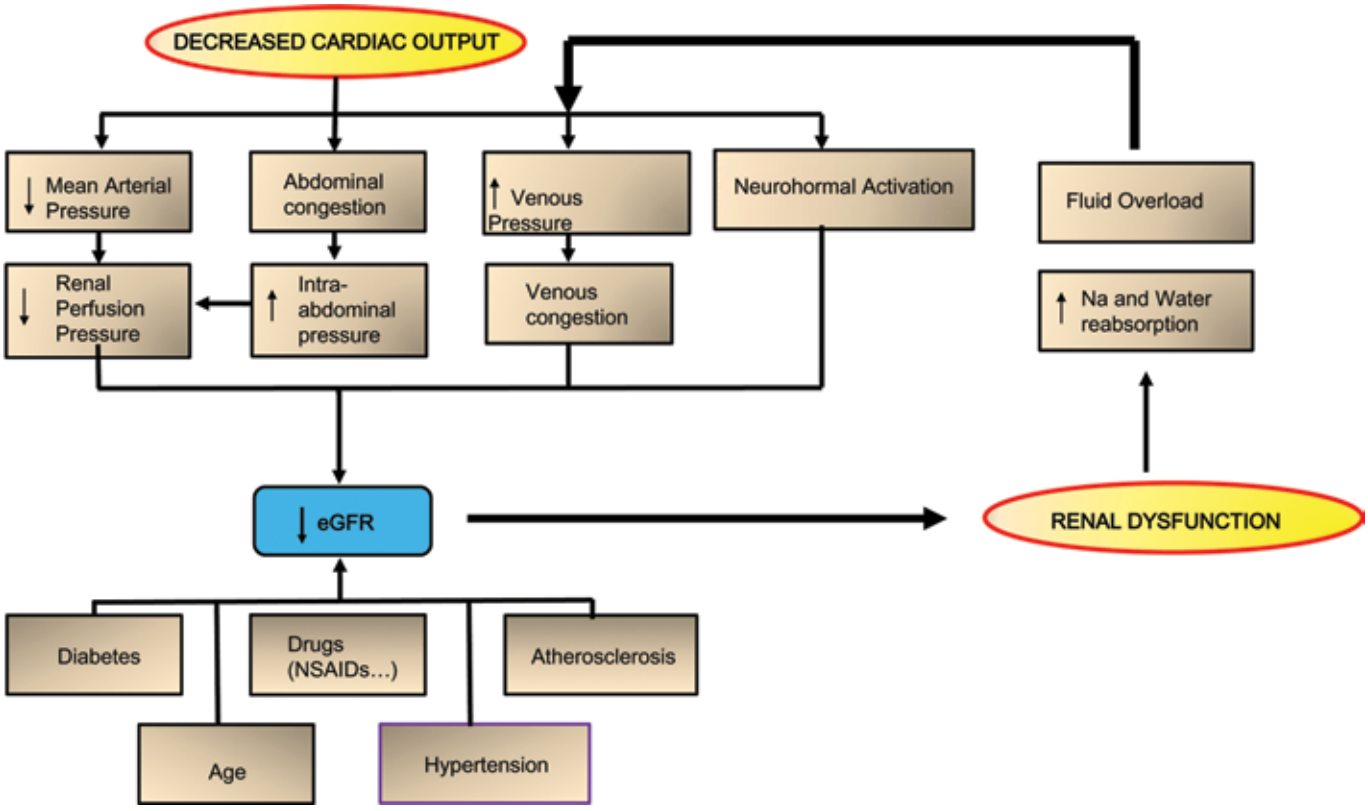


Fig. 1 - The pathogenesis of systemic congestion in heart failure. eGFR = estimated glomerular filtration rate; NSAIDs = nonsteroidal antiinflammatory drugs.

What is the epidemiological and prognostic importance of congestion in HF?

Heart failure is a major clinical issue, which imposes a heavy social and economic burden on health care systems in developed countries. In fact, it directly causes approximately 1 million hospital admissions every year in the United States, with most of them being due to either de novo HF or rapid decompensation of chronic HF (acutely decompensated HF [ADHF]) (1). Prognosis after hospitalization for HF is poor, with 30-day readmission rates of 27% (2) and 25% to 35% mortality at 1-year follow-up (3).

Fluid overload (FO), clinically evident as systemic and/or pulmonary congestion, represents the most frequent cause of hospitalization in this clinical setting, plays a central role in the progression of HF and has a major negative prognostic impact (4, 5). Since most of the patients admitted for ADHF are currently discharged without a clinically relevant improvement of congestion, it is not surprising that the proportion of patients who need readmission in the short term remains remarkably high, reaching 30% or more within 90 days (6).

The negative impact of congestion on patients' prognosis adds to that of worsening renal function (WRF) (7). Moreover, renal congestion is thought to play a key role in the progression of the syndrome, through its negative effects on both cardiac and renal function (8, 9).

What is the pathophysiology of systemic and renal congestion in HF?

The pathogenesis of systemic congestion in HF is complex (Fig. 1), and the role of the kidney is central. On the one hand, the kidney may significantly contribute to the pathogenesis of FO. In fact, as a result of the compensatory mechanism to HF, several neurohormonal pathways (e.g., sympathetic nervous system [SNS], renin-angiotensin-aldosterone system [RAAS], vasopressin etc.) are up-regulated, leading to excess water and sodium retention (9, 10). On the other hand, GFR and renal perfusion pressure are negatively affected by the increased venous pressure secondary to congestion (10). Renal perfusion pressure (i.e., the difference between mean arterial pressure and renal venous pressure), as well as the transglomerular pressure gradient, are decreased, while renal interstitial pressure is increased (11). As a consequence, a vicious cycle of sodium/water retention and WRF is established. The effects of increased renal venous pressure on GFR and renal blood flow are more important than those of equivalent decreases in mean arterial pressure or cardiac output, which are typically observed only in the most advanced stages of HF (10-13). Venous congestion due to high right-sided filling pressures has been reported as an independent predictor of both reduced eGFR and mortality (14, 15). Finally, FO and renal congestion may promote inflammation, by increasing vascular dysfunction through endothelial activation (16).

What is the rationale for diuretic therapy in HF?

Adequate control of systemic congestion along with maintenance and improvement of renal function represents a key target of patient management in HF. In fact, decongestion, when assessed on the basis of the observed degree of hemoconcentration, is associated with decreased all-cause mortality, cardiovascular mortality and rehospitalization rates, even when associated with transient WRF (17-19). On these grounds, current guidelines suggest that decongestion should be attempted through diuretic therapy (20-22) (Tab. I). Diuretics, essentially loop diuretics, are utilized in more than 90% of patients with HF to obtain urinary output increase, dyspnea relief and weight loss (22), despite the fact that a formal demonstration of their effect on hard outcomes is lacking (9).

When can a patient with HF be defined as diuretic resistant?

Diuretic treatment of systemic and pulmonary congestion can be ineffective in some patients with HF – a condition commonly referred to as *diuretic resistance or refractoriness.* However, the lack of an operational definition makes it difficult to define the exact incidence of this problem. It is thought that about one third of patients with HF, especially in the phase of acute decompensation, may present with apparent diuretic refractoriness (23). The classical definitions of diuretic resistance, although underscoring the qualitative concept of inadequate decongestion despite an intensive and escalating diuretic use (9, 24), do not provide formal indications about diuretic doses and modalities of administration. More precise definitions proposed in the past were based on variables not easily available at the bedside; examples drawn from the literature include a fractional sodium excretion lower than 0.2% (25), or the failure to excrete at least 90 mmol of sodium within 72 hours under treatment with furosemide 160 mg i.v. b.i.d. (26). More recently, different metrics have been proposed, such as weight loss per unit of 40 mg of furosemide (or equivalent) (27, 28), net fluid loss per milligram of loop diuretic (40 mg of furosemide or equivalent) during hospitalization (29) or the natriuretic response to furosemide expressed as the ratio of urinary sodium to urinary furosemide (30). However, although an objective measurement of the diuretic response in terms of efficiency (i.e., the ratio of the decongestive effect to the diuretic dose) may be appealing, these new metrics should undergo extensive investigation and validation before they can be applied routinely. Furthermore, not enough consideration has been devoted to nonpharmacological factors that can decrease the efficacy of diuretic therapy, independent of seemingly adequate doses and modalities of administration.

Diuretic response is mainly evaluated based on urinary output; yet many factors, not always related to diuretic therapy per se, or which may even be independent of the diuretic dose, are known to negatively affect the final result in terms of decongestion. Inasmuch as a number of these factors represent causes of "pseudoresistance" (Tab. II) via

TABLE I - European Society of Cardiology 2016 guidelines on diuretic use and ultrafiltration in heart failure

	Class	Level
Diuretics are recommended to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion	I	B
Diuretics should be considered to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion	IIa	B
Diuretics are recommended in congested patients with HFpEF or HFmrEF to alleviate symptoms and signs	I	B
A thiazide diuretic (or if the patient is being treated with a thiazide diuretic, switching to a loop diuretic) is recommended	I	C
Intravenous loop diuretics are recommended for all patients with AHF admitted with sign/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of i.v. diuretics	I	C
In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics, the initial recommended dose should be 20-40 mg i.v. furosemide (or equivalent); for those on chronic diuretic therapy, initial i.v. dose should be at least equivalent to oral dose	I	B
It is recommended to give diuretics either as intermittent boluses or as a continuous infusion, and the dose and duration should be adjusted according to the patient's symptoms and clinical status	I	B
Combination of loop diuretic with either thiazide-type diuretic or spironolactone may be considered in patients with resistant edema or insufficient symptomatic response	IIb	C
Ultrafiltration may be considered for patients with refractory congestion, who have failed to respond to diuretic-based strategies	IIb	B
Renal replacement therapy should be considered in patients with refractory volume overload and acute kidney injury	IIa	C

AHF = acute heart failure; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFmEF = heart failure with mid-range ejection fraction.

TABLE II - Causes of diuretic resistance and pseudoresistance

Compliance and dietetic factors	Acute and chronic comorbidities	Cardiac factors	Pharmacological causes
Unrestricted water intake	Pneumonia	Arrhythmias	NSAIDs
Unrestricted sodium intake	Pulmonary embolism	Hypertension	Negative inotropes
No monitoring of body weight	COPD	Ischemia	Inadequate diuretic therapy
	Thyroid disease	Valvular	
	Anemia	Endocarditis	
	Surgical stress		
	AKI		
	CKD		

AKI = acute kidney injury; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; NSAIDs = nonsteroidal antiinflammatory drugs.

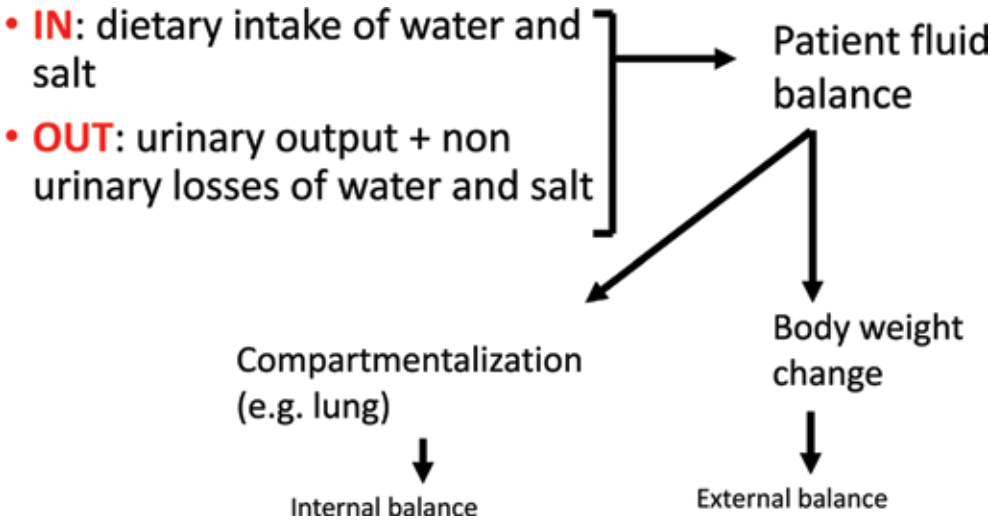


Fig. 2 - Decongestive therapy in heart failure: factors involved in the achievement of an adequate diuretic effect.

nonpharmacological mechanisms, they should be carefully identified before a patient may be regarded as truly diuretic resistant. In fact, while urinary output is a key component of the fluid balance (Fig. 2), it is not the unique parameter of diuretic effectiveness. As a more physiologically sound approach, which is also more useful in daily clinical practice, weight change is a key clinical variable to be monitored because it is a direct expression of the difference between fluid input and output. For example, a common cause of pseudoresistance to diuretic therapy is represented by inadequate control of sodium and water intake, which occurs when clinicians pay attention uniquely to urinary output while neglecting the patient's external fluid balance (Fig. 2). In fact, a high fluid intake may blunt the decongestive effect of diuretic therapy, despite "adequate" daily urine output; moreover, in the specific case of increased water intake in patients with HF, the risk of hyponatremia is also highly increased. However, no clear-cut indications exist about salt and water restriction in HF, due to controversial results from the available studies (31). This uncertainty is likely due to inhomogeneous patient characteristics, severity of HF, study design and amount of salt/water restriction, rather than to a true lack of efficacy of fluid restriction per se. Thus, it seems prudent to monitor sodium and water intake (32), tailoring individual needs according to the severity of HF and congestion and their response to diuretic therapy. When causes of pseudoresistance are reasonably excluded, a close review of the adequacy of diuretic therapy in terms of adherence to the classical pharmacodynamics and pharmacokinetic principles should be started.

What are the mechanisms and the pharmacological determinants of diuretic efficacy?

The inadequate consideration of basic pharmacokinetic and pharmacodynamic principles of diuretic therapy is usually the main source of diuretic resistance in patients with HF. From a practical standpoint, potential pharmacokinetic and pharmacodynamic mechanisms of resistance should therefore be evaluated separately (Figs. 3 and 4) (9, 33-36). The coexistence of impaired or worsening kidney function is the most common cause of pharmacokinetic resistance (36). In fact, an impaired renal function compatible with acute or chronic kidney disease (CKD) can be found in a high proportion of patients with HF

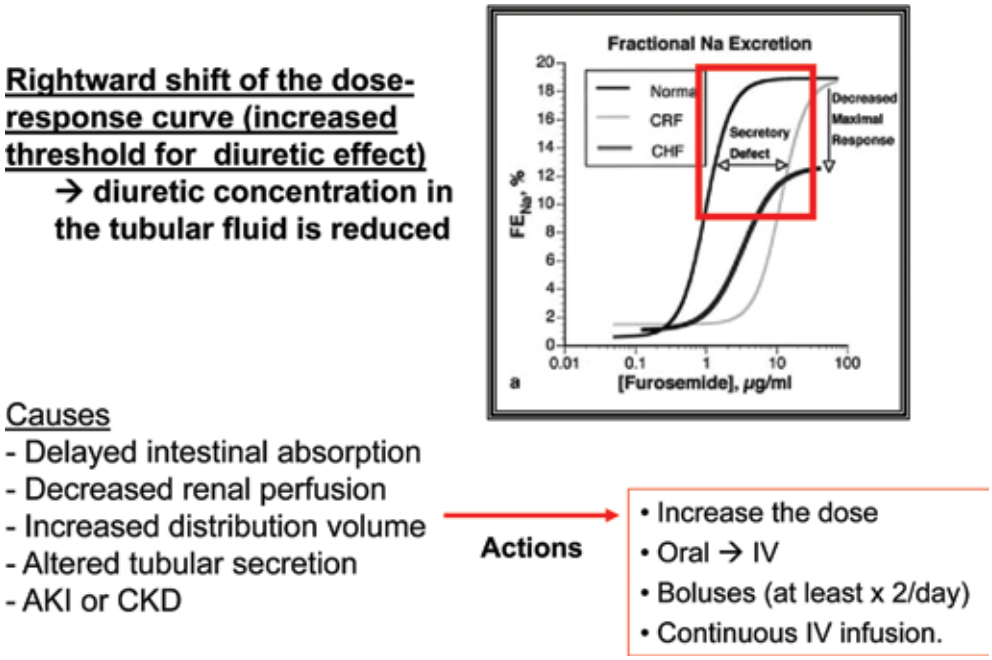


Fig. 3 - Pharmacokinetic mechanisms of diuretic resistance (reduced drug availability at site of action). AKI = acute kidney injury; CHF = congestive heart failure; CKD = chronic kidney disease; CRF = chronic renal failure; FE_{Na} = fractional excretion of sodium.

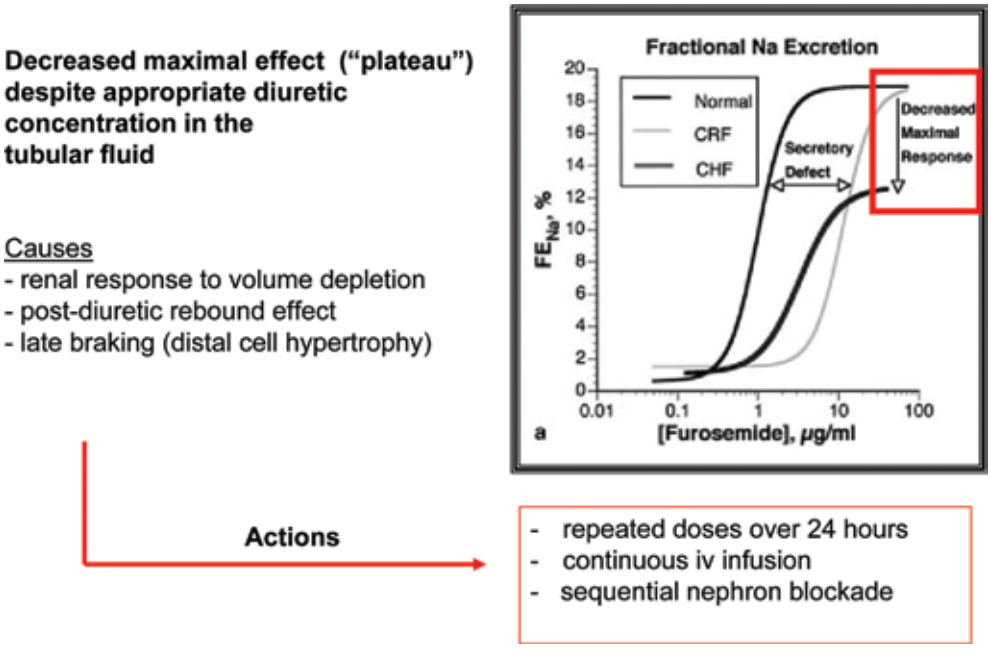
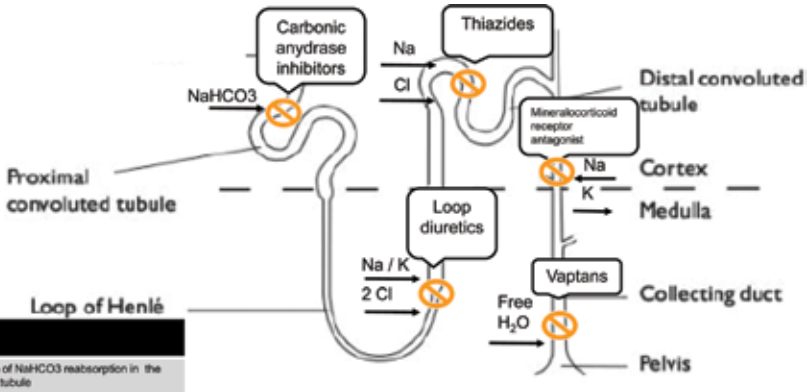


Fig. 4 - Pharmacodynamic mechanisms of diuretic resistance (impaired tubular response). CHF = congestive heart failure; CRF = chronic renal failure; FE_{Na} = fractional excretion of sodium.

(37-39). Other conditions commonly associated with poor diuretic responsiveness in observational studies include diabetes mellitus, high BUN levels and low systolic blood pressure (27, 29). However, these conditions likely represent markers of impaired kidney function, inappropriate renal response to congestion and/or severity of illness, rather than true direct resistance factors.

Based on the characteristic sigmoidal dose–response curve of both thiazides and loop diuretics (40), to overcome potential pharmacokinetic sources of resistance, it is necessary to achieve the *threshold* dose and maintain the *plateau* (or *ceiling*) effect. On the other hand, to overcome potential pharmacodynamic mechanisms of resistance, it is also required that the drug effect be maintained beyond its site of action (29). A thorough knowledge of the mechanisms of action and proper modes of administration of diuretics is thus required to optimize the diuretic effect. Because diuretics are natriuretic drugs, they act through the inhibition of specific sodium transport mechanisms in different and sequentially located anatomic tubular segments of the nephron (Fig. 5).



Carbonic Anydrase inhibitors	Inhibition of NaHCO3 reabsorption in the proximal tubule
Loop diuretics	Blocking the Na+-K+-2Cl- co-trasporter in the thick ascending limb of Henle's loop
Thiazides	Inhibiton of Na and Cl reabsorption in the distal tubule
Mineralocorticoid receptor antagonist	Inhibiton of ENaC channels and Na resorption in the collecting duct
Vaptans	Blocking the V2 vasopressin receptor

Fig. 5 - Sites of action of diuretics.

This concept sets the stage for the clinical classification of diuretics and their rational use in combination – i.e., the so-called sequential nephron blockade (40) (Fig. 5).

Inasmuch as diuretics interact with their molecular targets on the luminal side of the tubule, appropriate delivery to their intratubular sites of action plays a key role in determining diuretic response. Following intestinal absorption or i.v. administration, diuretics are transported by albumin in the bloodstream, therefore they are not filtered at the glomerulus. They are moved to the basolateral (capillary) side of the proximal tubular cells, and are actively secreted in the tubular lumen by the organic anion transport system located in the S2 segment (41).

The dose of a given diuretic should be adequate in terms of attaining the threshold (i.e., the minimum dose reaching a tubular concentration of the drug sufficient to start sodium and water excretion), and timing and mode of administration should allow the maintaining of a maximum natriuretic effect (the ceiling or plateau of diuretic response) (41). A number of pathological conditions are characterized by a rightward shift of the dose–response curve (i.e., by a higher threshold for starting the diuretic effect), due to a decreased diuretic concentration in the tubular lumen at a given dose. Thus, delayed intestinal absorption of the drug due to parietal edema and/or gut hypoperfusion, increased volume of distribution, competition for tubular secretion by other organic acids and inadequate timing and mode of administration, as well as impaired kidney function, will negatively affect the diuretic and natriuretic effect (9, 33-36, 40).

Diuretic efficacy in this case can be improved by increasing the dose, by shifting to i.v. administration (average bioavailability of loop diuretics after oral administration is about 50%) and by fractioning the total 24-hour dose based on half-life (at least twice-a-day boluses), or by choosing the continuous infusion modality instead of divided i.v. boluses (40).

Mechanisms of tubular adaptation to the diuretic and natriuretic effect represent the most common source of pharmacodynamic resistance to loop diuretics (9, 33-36). These mechanisms usually result in a decreased maximum diuretic and natriuretic effect, despite seemingly adequate drug concentrations in the tubular lumen (41). Three possible mechanisms are mainly involved: namely, the renal response to hypovolemia or volume depletion, the postdiuretic rebound effect ("early braking") and the "late braking" phenomenon (9, 33-36, 40).

The first mechanism is based on the complex array of hemodynamic and neurohumoral mechanisms that are usually activated following volume depletion and hypovolemia (e.g., decreased GFR and/or changes in Starling forces in the peritubular capillaries, leading to increased proximal reabsorption of sodium and water due to SNS and RAAS activation, and secondary hyperaldosteronism and Antidiuretic hormone (ADH) activation with ensuing increased sodium and water reabsorption in the distal nephron). These mechanisms are commonly activated in HF, and are maximized when an overly vigorous diuretic effect causes a mismatch between the rate of sodium and water removal from the vascular compartment and the vascular refilling rate from the interstitium (36). The second mechanism is observed when a diuretic with a short half-life (typically, a loop diuretic) is given only once a day, or even every other day. Urinary output and sodium excretion will be increased for the first few hours following diuretic administration, while renal adaptive mechanisms aimed at increasing sodium and water reabsorption will counterbalance this effect during the following hours; indeed, in the case of loop diuretics, both proximal and distal sodium and water reabsorption will be increased due to the changes of peritubular hemodynamic pressure secondary to RAAS activation. Fractioning the total 24-hour diuretic dose based on drug half-life is a possible solution for this problem. In the third case, the chronically increased sodium delivery to distal nephron segments, due to a protracted treatment with loop diuretics, leads to a compensatory cell hypertrophy in the distal tubule, with an increased number of Na-Cl cotransporter and Na/K ATPase units that ultimately result in increased sodium reabsorption at this level (41).

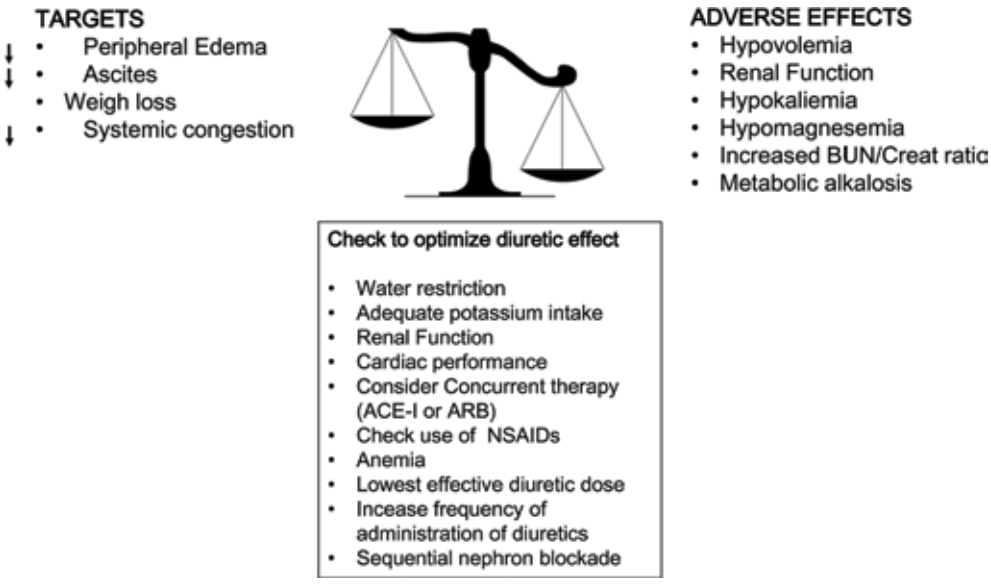


Fig. 6 - Optimization of diuretic therapy in heart failure. ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BUN = blood urea nitrogen; Creat = creatinine.

The combination of diuretics with different mechanisms and sites of action ("sequential nephron blockade") – e.g., a loop diuretic plus metolazone or hydrochlorothiazide, plus spironolactone (and possibly acetazolamide in selected cases) – will allow the reestablishment of diuretic efficacy (9, 33-36). Finally, it is to be underscored that optimization of diuretic therapy should be based on a careful evaluation of different factors influencing diuretic effect (Fig. 6), to facilitate the achievement of targets while avoiding adverse effects.

Are loop diuretics more effective when administered as a continuous infusion in patients with HF?

The treatment of ADHF requires the use of loop diuretics. Indeed, prompt i.v. treatment with these drugs at appropriate doses in this setting has proven to be very effective in relieving dyspnea and congestion. On the other hand, no clear-cut indications exist in the literature concerning a putative advantage of the treatment of patients with ADHF by continuous infusion of loop diuretics as compared with intermittent i.v. boluses.

In fact, considering the short half-life of furosemide, continuous infusion of this drug may have the following benefits (42-44):

- lower risk of *rebound* sodium retention (by ensuring maintenance of the ceiling in the dose–response curve, and thus of a prolonged natriuretic effect);
- greater efficacy (higher absolute urinary output and natriuresis) and efficiency (comparable urinary output and sodium excretion at lower drug excretion rate) (45);
- smaller fluctuations of intravascular volume status with reduced neurohumoral activation and lower incidence of WRF (46);
- lower ototoxicity (47).

Although continuous infusion of loop diuretics may appear as a pathophysiologically sound option in patients with ADHF, the results of the Diuretic Optimization Strategies Evaluation (DOSE) trial (47) did not show a significant difference, in terms of efficacy and safety, between continuous infusion and intermittent i.v. bolus administration. However, during the first 72 hours after randomization, the continuous infusion group received a lower cumulative diuretic dose; moreover, the frequency of additional thiazide administration (i.e., treatment failure as per protocol) was significantly lower in this group. Another small randomized trial (48) showed that the patients in the continuous infusion arm had greater cumulative urine output and lower plasma B-type brain natriuretic hormone values than the patients in the intermittent bolus arm at the end of the study period; although the increase in sCr and BUN values was greater in the former group, the incidence of acute kidney injury (AKI) was not different between the 2 treatment arms. Finally, 2 recent meta-analyses (49, 50), neither of which included the study by Palazzuoli et al (48), reached opposite conclusions concerning the efficacy of continuous as opposed to intermittent i.v. administration of loop diuretics. Both the slightly different criteria used for study selection and a pronounced heterogeneity among the studies included could partially explain the different results of the 2 meta-analyses.

When a continuous infusion is chosen, a loading dose has to be given to reach an adequate diuretic concentration more quickly at the site of action (41). However, in patients requiring lower cumulative doses, a large initial bolus may not be necessary to achieve a high tubular concentration (51); moreover, avoiding high-dose boluses may result in a lower risk of ototoxicity.

Is the use of diuretics with different mechanisms of action indicated in patients with HF in the case of diuretic resistance?

The optimization of diuretic therapy according to basic pharmacokinetic and pharmacodynamic principles may enable the improvement of its efficacy (Figs. 3 and 4). The use of

doses of loop diuretics still represents the mainstay of the therapeutic approach to congestion. However, the combination of loop diuretics with other drugs acting at different tubular sites may contribute to overcome the most common pharmacodynamic sources of resistance to loop diuretics (40). The addition of thiazides, which increase sodium excretion by blocking sodium and chloride reabsorption distally with respect to the site of action of loop diuretics, may diminish the negative impact of both early and late braking; thiazides have in fact a longer half-life compared with the most commonly used loop diuretic (furosemide), and may specifically may blunt the compensatory response due to the hypertrophy of distal tubular cell (40). Metolazone is the most widely used thiazide for this purpose, even in patients with CKD. Moreover, inasmuch as in patients with HF, sodium reabsorption is typically increased in the proximal tubule, the addition of acetazolamide may further potentiate the natriuretic effects of the combination of loop and thiazide diuretics (25). Finally, the addition of a mineralocorticoid receptor antagonist (MRA), such as spironolactone, at daily doses of at least 50-75 mg may blunt the excess sodium reabsorption in the collecting duct due to secondary hyperaldosteronism (52, 53). MRAs can also be added to the combination of loop and thiazide diuretics (54, 55).

Apart from the advantages deriving from sequential nephron blockade in terms of increased sodium and water excretion, some adverse effects of diuretic therapy can be reduced by the combination approach. Both loop and thiazide diuretics increase the risk of hypokalemia, as they increase potassium excretion, and the addition of an MRA can exert a potassium-sparing effect. Finally, acetazolamide can decrease the high incidence of metabolic alkalosis associated with loop and thiazide diuretics in HF patients (56), by promoting the excretion of sodium bicarbonate.

Vasopressin receptor antagonists ("vaptans") represent another class of drugs that, by promoting free water diuresis ("aquaretics"), can be useful to mitigate congestion in combination with loop diuretics or sequential nephron blockade in patients with advanced chronic HF or ADHF. Tolvaptan, conivaptan and lixivaptan have been tested in this clinical setting. At present, however, only tolvaptan and conivaptan have been approved by the US Food and Drug Administration for the treatment of hyponatremia associated with increased extracellular fluid volume, a condition that includes congestive HF, only in the United States; conversely, the European Medicines Agency has approved the use of tolvaptan uniquely for the treatment of hyponatremia associated with the syndrome of inappropriate Antidiuretic hormone (ADH) secretion (57).

The use of tolvaptan has been examined in 3 randomized, double-blind, placebo-controlled clinical trials enrolling patients with advanced HF (58-60). While treatment with this drug was associated with greater weight loss, more relevant reduction of dyspnea and a significant increase in serum sodium without detrimental effects on kidney function, it had no impact on all-cause mortality or hospitalization rates at 10-month follow-up.

In patients with congestive HF, a short-term treatment with conivaptan, given as continuous infusion, has proven effective in decreasing heart filling pressures (61). Moreover, another study reported a significant increase in urine output at 24 and 48 hours during infusion of different doses of conivaptan, compared with placebo, given on top of standard loop diuretic therapy (62).

Lixivaptan has also been studied in patients with HF in a small randomized study (63), and has been shown to promote a dose-related increase in urine output compared with placebo. However, data from the larger BALANCE study (64) are awaited.

In conclusion, although a short-term treatment with a vasopressin antagonist can help in decreasing congestion in patients hospitalized with advanced decompensated HF, further data are needed to clarify whether this potential advantage translates into better long-term outcomes in terms of survival and/or rehospitalization rates.

Is hypertonic saline indicated in patients with HF to overcome diuretic resistance?

Long-term and high-dose treatment with loop diuretics in patients with HF, particularly in the acute decompensated phase, has been blamed for increasing negative outcomes in terms of both WRF (65) and survival (65-68). Although this belief is based uniquely on retrospective studies, and is partially contradicted by evidence from 1 randomized controlled trial (47) and 1 systematic review (69), several pathophysiological mechanisms have been invoked to explain putative harmful effects of the treatment with high-dose loop diuretics in this clinical setting (70). In fact, a fall in effective arterial blood volume may trigger excess stimulation of the SNS and RAAS, renal hypoperfusion, activation of the tubuloglomerular feedback with ensuing vasoconstriction of the afferent arteriole and decreased GFR. Moreover, secondary hypokalemia and hypomagnesemia may promote an increased incidence of arrhythmias. Furthermore, relative kidney hypoperfusion and the resulting changes in Starling forces at the level of the proximal tubule can increase sodium reabsorption at this level, thus participating in the development of diuretic resistance.

Based on the favorable effects in terms of improved hemodynamic indexes and increased urine output observed in patients with septic shock (71) and in patients undergoing major heart surgery (72-75), in recent years, some investigators have tested a combination of diuretic treatment with the administration of repeated boluses of hypertonic salt solution (HSS; 1.4%-4.6% NaCl) in patients with advanced HF and reduced response to diuretic therapy. The rationale of this approach (76), although counterintuitive and seemingly paradoxical, is based on the idea that a rapid infusion of HSS would favor vascular refilling, thus decreasing baroreflex-dependent SNS and RAAS overactivity. It would also ameliorate kidney perfusion and favor diuretic transport to sites of tubular secretion, also blunting the excess sodium reabsorption at the level of the proximal tubule. Moreover, by increasing sodium chloride delivery to the distal nephron, HSS would promote the restoration of the efficacy of loop diuretics. Further putative mechanisms may be represented by decreased circulating levels of inflammatory cytokines (TNF-α, IL-6), as well by an inotropic effect directly triggered by plasma hyperosmolarity, or indirectly mediated by the activation of the sodium-calcium exchanger.

Two single-blind randomized studies (77, 78) compared a strategy based on a twice-a-day 30-minute furosemide infu-

sion (dose ranging from 500 to 1,000 mg), combined with the infusion of HSS 150 mL (1.4%-4.6% NaCl according to baseline serum sodium concentration), with a strategy based on twice-a-day furosemide boluses (500-1,000 mg) without HSS; both treatments were followed for 6-12 days until resolution of acute HF. In the second study (78), the investigators also tested, with a factorial design that included the 2 strategies mentioned above, the effects of a long-term sodium dietary restriction (80 vs. 120 mmol NaCl/day). Both studies reported an increase in cumulative urine and sodium output and a decrease in sCr and length of hospital stay, as well higher serum sodium values at discharge, in the patients treated with furosemide plus HSS compared with those treated with furosemide alone. Moreover, in the second study (78), a less restricted dietary sodium intake (120 mmol/day) was associated with lower rehospitalization rates at a 30-day follow-up.

Despite these intriguing results, a closer inspection of the study protocol for both studies reveals several controversial points. Firstly, the definition of refractory HF employed in both trials was questionable. Secondly, the average daily dose of loop diuretics prior to randomization was not specified in either group; moreover, the investigators did not provide the median (interquartile range) dose of loop diuretic in the active phase of both trials. Thirdly, in the furosemide-only arm, the loop diuretic was administered as divided boluses, thus with a potentially less effective impact, compared with the furosemide plus HSS arm where the loop diuretic was infused over a longer time interval. Finally, notwithstanding a greater urine output in the furosemide plus HSS vs. the furosemide-only arm, weight loss was not different between the 2 groups.

However, a large single-blind randomized trial, performed in 1,771 patients with NYHA class III HF during hospitalization due to acute decompensation (79), reported results in agreement with those of the previous smaller studies (77, 78) using a similar protocol based on a lower furosemide dose (250 mg) given as 30-minute infusions combined with 150 mL of either HSS or normal saline (placebo). In the furosemide plus HSS and 120 mmol/day NaCl arm, the investigators observed not only a greater urine and sodium output, as well as a shorter hospital stay, but also a greater survival and a lower rehospitalization rate at an average 57-month follow-up.

Furthermore, 2 double-blind randomized controlled studies by the same investigators using the same protocol (80, 81) reported that furosemide plus HSS combined with 120 mmol/day dietary NaCl intake in patients with advanced HF was associated with a greater urine and sodium output and improved kidney function, as well as a greater decrease in circulating B-type brain natriuretc hormone levels and bioimpedance indexes, compared with furosemide alone combined with a greater NaCl dietary restriction at 80 mmol/day. Similar results, together with improved echocardiographic indexes and decreased troponin levels, were obtained in patients with ADHF (82).

Finally, a small double-blind randomized study (83) reported a lower incidence of AKI, defined as a >0.3 mg/dL sCr within 72 hours of randomization, in patients treated with a variable i.v. furosemide dose plus divided boluses of 7.5% NaCl HSS, compared with patients treated with furosemide plus divided boluses of normal saline (placebo). It should be underscored that furosemide dose was decided according to the attending physician's discretion in each patient, and that its administration as divided i.v. boluses may not have been ideal. Furthermore, although the average furosemide dose was significantly lower in the HSS than in the placebo arm (120 vs. 160 mg/day, $p<0.001$), both these average doses and their dose range (80-120 mg/day and 120-160 mg/day, respectively) were clearly lower than those usually indicated in patients with "refractory" HF.

In conclusion, although a treatment strategy based on the combination of i.v. furosemide at appropriate dose combined with small i.v. boluses of HSS may appear as an interesting opportunity in patients with advanced decompensated HF, at present this approach should be considered experimental and therefore be limited to clinical research.

Is it worth adding low-dose dopamine in the case of diuretic resistance in patients with HF?

Dopamine is a vasoactive amine with renal vasodilating and natriuretic proprieties. By acting mainly on renal DA_1 and DA_2 receptors when infused at low doses (≤3 mg/kg per minute), it increases renal blood flow; moreover, it decreases sodium reabsorption in the proximal and distal tubules (84).

After an early report of increased natriuresis elicited by low-dose dopamine in a patient with HF (85), 2 small uncontrolled trials in the late 1990s suggested that adding low-dose dopamine to standard treatment with loop diuretics might be effective in increasing urine output in these patients while preserving renal function (84, 86).

However, the results from 3 recent randomized controlled trials seem to contradict earlier data. In the Dopamine in Acutely Decompensated Heart Failure (DAD-HF) study (87), a strategy based on the infusion of "low-dose" dopamine (5 μg/kg per minute) combined with low-dose furosemide (5 mg/hour) was not associated with greater urine output and symptom relief compared with a strategy based on high-dose furosemide (20 mg/hour) only, although the incidence of WRF was higher with the latter approach.

The subsequent DAD-HF II trial (88) compared low-dose dopamine plus low-dose furosemide with high-dose furosemide and low-dose furosemide, and found no significant differences in urine output at different time points or dyspnea relief, or any significant differences in hard outcomes; the incidence of WRF, evaluated at peak sCr, was also similar with the 3 treatment strategies.

Finally, the much larger Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF) trial (89), also failed to demonstrate greater urine output or decongestion, or any better hard outcomes, associated with diuretics plus low-dose (2 μg/kg per minute) dopamine or low-dose nesiritide compared with standard diuretic-only therapy.

In conclusion, solid evidence indicating a true efficacy of adding dopamine to standard diuretic therapy in patients with ADHF is lacking at present.

Are diuretic resistance and reduced or worsening renal function relevant for patients' outcomes?

Diuretic resistance is thought to be present in up to one third of patients hospitalized for ADHF. It is associated with impaired dyspnea relief, high risk of rapid progression of

HF, higher mortality following hospital discharge and higher hospitalization rates (9, 27, 28, 30), although such a negative prognosis may be at least in part due to a more severe underlying disease process and, in particular, AKI or CKD (90).

In general, 30%-60% of patients with HF fulfill the standard diagnostic criteria for CKD – i.e., an eGFR of <60 ml/min per 1.73 m^2 based on standard formulas such as the Modification of Diet in Renal Disease (MDRD) study and CKD-EPI (37). In the Acute Decompensated Heart Failure National Registry (ADHERE) database, including about 100,000 individuals, 30% of patients had sCr levels >2 mg/dL (38). The incidence of a new AKI episode was 20%-30% (91-95).

While the coexistence of CKD in patients with HF invariably portends a negative prognosis, the problem of WRF, especially in acute HF and in the course of diuretic therapy, is more complex. In fact, the terms *kidney dysfunction* and *worsening renal function* are commonly used in the cardiological literature to define a rather heterogeneous array of clinical conditions, characterized by nonspecific impairment of renal function and a condition similar to AKI, respectively. As kidney functional status directly impacts on clinical outcomes (96) and may heavily affect the therapeutic approach (97), the different methods used to evaluate renal function are likely to play a key role in the evaluation and care of patients with HF. In fact, although renal dysfunction in patients with HF can usually be classified within the broad and well-established categories of either AKI (98) or CKD (99), the evaluation of renal function in this clinical setting is not straightforward, due to the methodological limitations and interpretation problems of the different indexes employed.

Although different formal classifications of the cardiorenal link have been proposed, based on criteria such as timing (100) or pathophysiology (101), from a practical standpoint, 3 forms of kidney dysfunction can be identified at the bedside in ADHF, by integrating clinical presentation, time course and likely pathogenetic mechanisms:

a. A form of preexisting chronic kidney dysfunction, corresponding to classical CKD, for which standard definitions and classification criteria can be applied. Two cutoff points for eGFR can be set in this form: namely, below 60 ml/min per 1.73 m^2 down to 30 ml/min per 1.73 m^2 (National Kidney Foundation [NKF] stage III), and below 30 ml/min per 1.73 m^2 down to 15 ml/min per 1.73 m^2 (NKF stage IV) (99).
b. A form of rapidly WRF, which is typically observed in patients admitted for new-onset HF or acute decompensation of a previous condition of chronic HF. In this clinical setting, WRF displays strong temporal heterogeneity, as it can be already evident at admission, or may develop during the hospitalization period or even at a variable distance from the patients' discharge. Furthermore, its pathogenetic mechanisms may be considerably different (102, 103), as they may be related to the severity of congestion, to hemodynamic status (low cardiac output, intrinsic worsening of pump function, hypotension etc.), to preexisting kidney dysfunction, to drug treatment or to the administration of radiocontrast media; accordingly, its prognostic impact may also be variable, and not necessarily negative (104, 105).
c. A form of delayed-onset and progressive WRF, developing weeks or months after the patient's discharge following an ADHF episode (95, 106). Its mechanisms may be different from those hypothesized for classical AKI, and could reflect a progressive and irreversible nephron loss (95) with an important negative impact on patient outcomes (107, 108).

Clinicians are often reluctant to use high doses of loop diuretics, based on the results of observational studies, mainly retrospective in nature, suggesting that the administration of high-furosemide-equivalent doses may be associated with WRF (109). However, a number of recent studies indicate that the prognostic impact of an increase in sCr may not invariably be negative, as it is highly dependent on time of onset, the relationship with the treatment of congestion or the persistence of congestion at the time of hospital discharge (67). According to the literature data, the onset of WRF occurs after 3-4 days from admission on average, with wide variability (1-12 days); this widely variable time interval, particularly when compared with the average length of hospital stay (approximately 8-10 days), may reflect the development of different forms of WRF. In fact, earlier forms may mirror a negative trend in kidney function already present before admission, whereas other forms with later onset could possibly represent the consequence of mistreatment, in the form of either insufficient decongestion in the patients discharged without weight loss, or overzealous fluid depletion and ensuing hypovolemia due to excess fluid removal (39, 110, 111).

Whatever the clinical scenario for WRF, a strong relationship between WRF and CKD must be underscored, inasmuch as the latter often precedes, and is the main risk factor for, WRF (112). These complex heart–kidney links suggest that different forms of WRF can be better recognized based on a correct pathogenetic approach, rather than on a putative temporal relationship between renal and heart disease within the conceptual framework of the so-called cardiorenal syndrome(s), inasmuch as this distinction may have an impact on both therapy and outcomes. At variance with the results obtained in experimental models (103), in clinical practice it is often difficult to identify a precise temporal relationship between heart and kidney dysfunction (104) (e.g., cardiorenal vs. renocardiac syndromes) (100), particularly in patients with a long history of both heart and kidney failure. In fact, pathogenetic factors and mechanisms are common to both conditions, and are likely to be related to underlying advanced vascular disease, with adverse consequences progressing in parallel in both the heart and the kidneys (103).

What if diuretic resistance cannot be overcome by optimizing diuretic therapy in patients with HF: is ultrafiltration a rational approach?

Ultrafiltration is a mechanical way of achieving hemoconcentration based on the removal of isotonic plasma water by creating a pressure gradient across the semipermeable membrane of a dialysis filter (36, 113). Ultrafiltration has been advocated as an alternative strategy for the treatment of congestion in patients with HF, specifically in the case of diuretic resistance (114). Theoretically, compared with diuretic therapy, isolated ultrafiltration (IU) should allow a more predictable control of

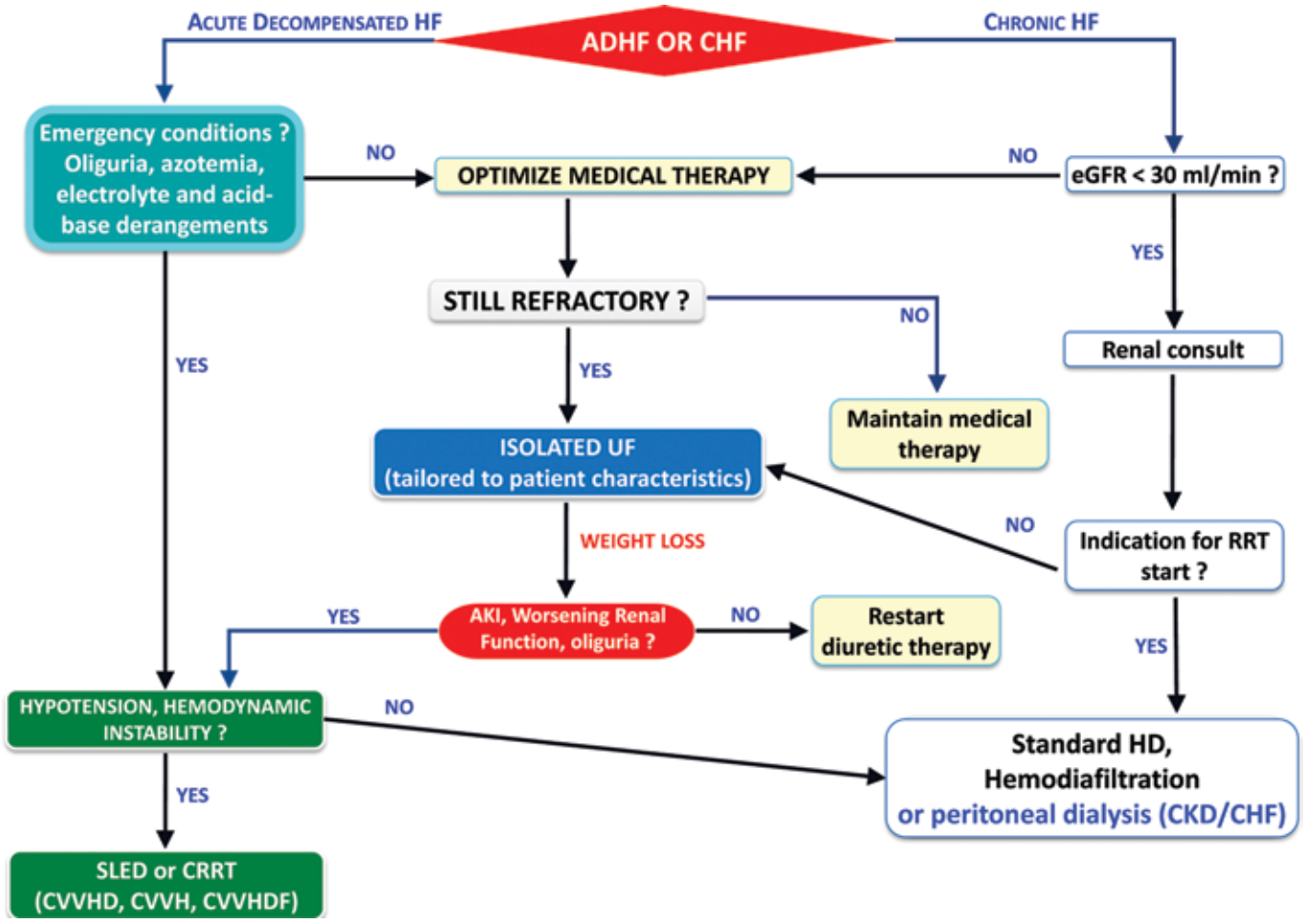


Fig. 7 - Algorythm for treatment of ADHF. ADHF = acutely decompensated heart failure; AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; CHF = congestive heart failure; CKD = chronic kidney disease; CRRT = continuous renal replacement therapy; CVVH = continuous venovenous hemofiltration; CVVHD = continuous venovenous hemodialysis; CVVHDF = continuous venovenous hemodiafiltration; HD = hemodialysis; HF = heart failure; RRT = renal replacement therapy; SLED = sustained low-efficiency dialysis; UF = ultrafiltration.

plasma water removal rate, which can be tuned to match the putative refilling rate from the interstitium; moreover, IU is credited with greater sodium depletion and a lesser degree of neurohormonal activation (114). Other hypothetical favorable effects (e.g., cytokine clearance or better control of electrolyte and acid-base status) are simply not allowed by the limited operational characteristics of this technique (36).

This strategy was initially tested in several small uncontrolled studies, with seemingly encouraging results in terms of decreased filling pressures, improvement of cardiac index and restored sensitivity to diuretics (36). The promising results of these studies prompted the planning of larger trials, such as the Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial (115) and the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial (68), aimed at demonstrating that IU is a more effective strategy than diuretic treatment to achieve adequate decongestion in patients with ADHF. Although it was concluded that IU was able to achieve a greater net fluid loss, together with a lower 90-day rehospitalization rate, without detrimental effects on kidney function, compared with "conventional" diuretic therapy, these studies were criticized for a number of methodological flaws (36). Two other randomized controlled trials failed to demonstrate that IU is superior to diuretic therapy (39, 107). In particular, while the AVOID-HF was terminated by the sponsor after recruitment of only 27% of the planned patient number, the CARRESS study showed no better clinical outcome in the ultrafiltration arm than in the optimized diuretic arm; moreover, GFR improved significantly in this latter group at 60 days.

On the whole, the available evidence, as well as even the most recent guidelines (20, 22) suggest that clinicians should adopt a very selective and targeted approach to performing ultrafiltration in patients with HF. Correct indications may be represented by emergency treatment in the presence of acute pulmonary edema with respiratory failure in oliguric HF, or congestion truly unresponsive to maximal and appropriate diuretic treatment (Fig. 7).

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