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REVIEW

Translational medicine

Renal sodium avidity in heart failure: from pathophysiology to treatment strategies

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Increased neurohumoral stimulation resulting in excessive sodium avidity and extracellular volume overload are hallmark features of decompensated heart failure. Especially in case of concomitant renal dysfunction, the kidneys often fail to elicit effective natriuresis. While assessment of renal function is generally performed by measuring serum creatinine–a surrogate for glomerular filtration-, this only represents part of the nephron's function. Alterations in tubular sodium handling are at least equally important in the development of volume overload and congestion. Venous congestion and neurohumoral activation in advanced HF further promote renal sodium and water retention. Interestingly, early on, before clinical signs of heart failure are evident, intrinsic renal derangements already impair natriuresis. This clinical review discusses the importance of heart failure (HF) induced changes in different nephron segments. A better understanding of cardiorenal interactions which ultimately result in sodium avidity in HF might help to treat and prevent congestion in chronic and acute HF.

Keywords Heart failure • Kidney • Diuretic • Glomerulus • Natriuresis • Sodium

Introduction

Approximately 90% of heart failure (HF) hospitalizations are associated with signs and symptoms of volume overload, which is associated with disease progression and worse prognosis.[1,2] While impaired renal sodium (Na^+) excretion secondary to neurohumoral upregulation is the primary abnormality, water movement passively follows Na^+ to keep osmolality in balance. Additionally, most patients have some degree of renal dysfunction, which impairs the 'reserve' available for the kidneys to respond to the insult posed by cardiac dysfunction.[3] The resulting imbalance leads to sodium accumulation followed by intravascular and interstitial volume retention, and eventually oedema as well as increased cardiac filling pressures.[4]

Sodium and water homeostasis

A typical Western diet contains approximately 12 g salt (sodium chloride or NaCl) per day, equivalent to ~4.5 g or ~200 mmol Na^+, which is almost completely absorbed in the gastro-intestinal system. From an evolutionary point of view, humans did not have much access to Na^+, so the neurohumoral systems (renin-angiotensin-aldosterone system and sympathetic nerve system) have evolved to retain $Na^+$and preserve effective circulatory volume. After an oral Na^+ load, its plasma concentration as well as plasma osmolality rises within half an hour and stimulates arginine vasopressin (AVP) release by the hypothalamus, stimulating anti-diuresis.[5] Subsequently, the rise in total body water is sensed by baroreceptors in the large (aortic arch, carotid sinus, atria) and small vasculature (pulmonary vasculature, liver, central nerve system, and renal afferent arteriole) to modulate urinary Na^+ and water excretion. Na^+ is freely filtered in the renal glomerulus, but only a tiny fraction is excreted in the urine as tubular Na^+ reabsorption exceeds 99%. Nevertheless, net renal Na^+ excretion is highly regulated to mimic dietary intake.[6]

Importance of renal function in heart failure

Chronic kidney disease (defined as an estimated glomerular filtration rate or GFR less than 60 mL/min/1.73 m^2) is present in up to 60% of

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ambulatory compensated HF patients.[7–9] Importantly, GFR is one of the strongest predictors of mortality and morbidity in HF patients, exceeding other well-known factors such as left ventricular ejection fraction or New York Heart Association functional class.[8] GFR is the net flow rate of plasma ultrafiltrate across the capillary membrane in the glomerulus. However, GFR, is a reflection of only the filtration function of the kidney while other important components of fluid homeostasis, such as renal tubular sodium and water avidity are not taken into account.

Especially in decompensated HF patients renal tubular function is of great interest.[10] Indeed, alterations in tubular function occur as a result of changes in neurohumoral activation and impaired tubular flow which definitely contribute to Na^+ retention. Furthermore, both filtration and tubular functions of the nephron must be maintained to permit the actions of treatments given to alleviate congestion in patients with HF. A large number of markers for renal tubular damage exist: kidney injury molecule–1, neutrophil gelatinase-associated lipocalin, and N-acetyl-beta-glucosaminidase.[11] Importantly, it has been demonstrated that in decompensated HF patients who experience a rise in serum creatinine, the degree of tubular damage is low.[12] Hence, worsening renal function is often not accompanied by tubular injury. However, if increased tubular markers are present, this almost certainly relates to poor outcomes.[13]

'Worsening' of renal function in heart failure

Patients with pre-existing chronic kidney disease are vulnerable to develop worsening renal function.[14,15] The prevalence of worsening renal function, traditionally defined as an ≥ 0.3 mg/dL increase in serum creatinine or > 15% reduction in GFR, ranges from 20% to 40% in acute HF.[8,16] Worsening renal function occurs typically within days of hospitalization, suggesting a direct causative effect of haemodynamic derangement associated with HF decompensation and/or iatrogenic treatment adjustments.[17] It is generally accepted that systemic haemodynamic derangements (elevated venous pressure, elevated intra-abdominal pressure, arterial blood pressure drops) rather than impaired cardiac output are the main drivers for GFR decline during acute decompensated HF.[3,18–22] Although, less understood, neurohumoral and inflammatory derangements also play a role in the complex pathophysiology of worsening renal function. Whereas baseline GFR is invariably linked to worse outcomes, recent studies about the prognostic value of worsening renal function in the setting of acute decompensated HF are mixed.[18,21,22] Indeed, when accompanied by successful treatment of volume overload, short-time declines in GFR even track with better prognosis.[23,2] Therefore, worsening renal function might merely reflect the result of effective decongestion–sometimes indicated by haemoconcentation–as well as intensified therapy with angiotensin-converting enzyme–inhibitors (ACE-I) or angiotensin receptor blockers (ARB). In contrast, worsening renal function might also be the result of persistent volume overload and/or neurohumoral derangements.[2,14] The latter being a reflection of the inability of the kidneys to preserve Na^+ homeostasis, which has been consistently associated with higher mortality and more frequent readmissions in HF. To conclude, GFR has proven to be a very important prognostic marker, but therapy should not be tailored to GFR to improve outcome.

Understanding the kidney in HF; different nephron segments

The kidneys' function is to clear toxins and waste products as well as to maintain the body's fluid- and electrolyte homeostasis and to preserve tissue perfusion. Hence, the kidneys must filter a sufficient–rather fixed–amount of blood per time from the renal glomerular capillaries into Bowman's capsule (filtration function) and precisely regulate tubular water and solute reabsorption (tubular function). These tasks are performed by different, highly specialized segments of the nephron.

Glomerulus

GFR depends on hydrostatic and colloid osmotic pressure differences between glomerular capillaries and Bowman's space (Starling forces), as well as the number of functional glomeruli.[10] Alterations in glomerular Starling forces are mainly the result of changes in hydrostatic pressure since the colloid osmotic pressure in the afferent arteriole is stable. In normal circumstances, renal perfusion or renal blood flow (RBF) is around 20% of cardiac output, and determined by the difference between renal arterial and venous pressure, the intra-abdominal pressure and renal vasculature resistance. An important feature of the renal mirco-circulation is *autoregulation*, which tries to keep GFR within narrow limits by adjusting the resistance of the afferent arterioles in response to renal arterial pressure and flow fluctuations through the nephron (*Figure 1*). First, a decrease in mean arterial blood pressure will lead to redistribution of blood volume to preserve kidney perfusion.[11] A second mechanism called 'tubuloglomerular feedback' protects the glomerulus from hyperfiltration by keeping chloride (Cl^-) load in Henle's loop at a constant level.[12] An increase in GFR will increase the delivery of Cl^- to macula densa cells. This stimulates paracrine release of adenosine which in turn induces vasoconstriction of the afferent arteriole and restores GFR.[13,14] Additionally, increased filtration in the glomerulus is met by increased reabsorption in the proximal renal tubules through a second feedback mechanism: 'glomerulotubular balance'.[15] Finally, because of the high filtration coefficient of the glomerular filtration barrier along the length of the glomerular capillaries, the GFR is relatively well maintained when the RBF drops, until the filtration equilibrium is reached. This will result in an increase in the filtration fraction, even without neurohumoral interference.[24] Indeed, when RBF is increased vs. reduced in the face of a preserved GFR, the ratio of GFR/RBF or filtration fraction, will be altered. Hence, two patients with similar GFR can exhibit a different filtration fraction and renal tubular Na^+ handling (*Figure 2*).

Furthermore, numerous other factors contribute to an impaired GFR in HF. First, there is a lower number of functionally active glomeruli. Second, neurohumoral activation in HF contributes to both low RBF and high filtration fraction, through increased systemic and local levels of angiotensin II. Angiotensin II stimulates

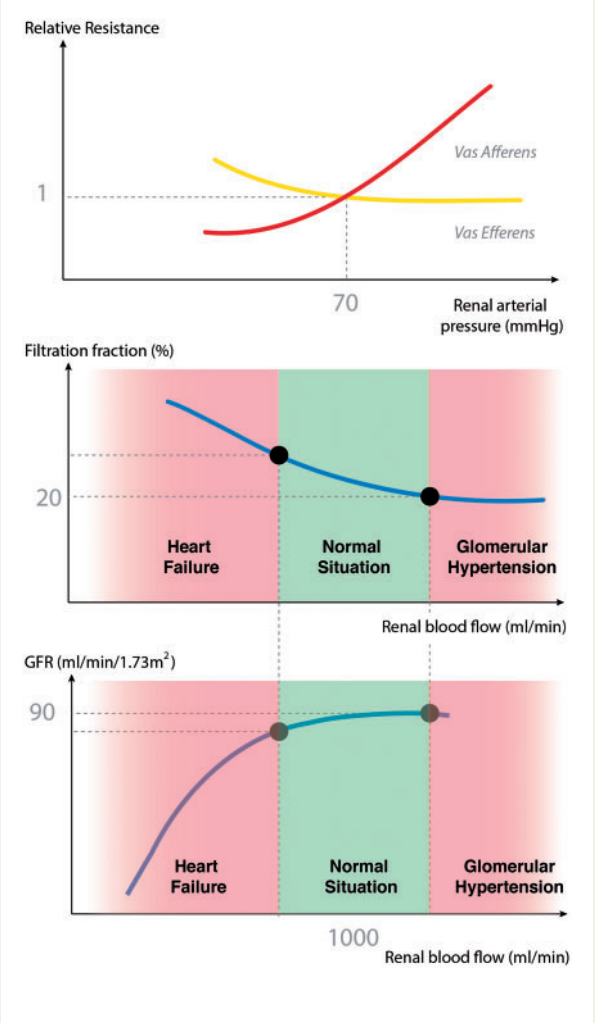

Figure 1 Relationship between filtration fraction and the glomerular filtration rate (GFR). The kidney tries to preserve the GFR with changes in filtration fraction over a wide range of arterial pressures by altering the resistance of the afferent and efferent arteriole.

vasoconstriction, predominantly in the efferent arteriole.[19,25] Third, backward failure due to increased central venous pressure is associated with decreased RBF and deterioration of GFR.[20–23] Several reports have confirmed that increased renal venous pressure decreased RBF accompanied by an increase in filtration fraction up to 60%.[2,24,26,27] Fourth, increased intra-abdominal pressure, compromised capacitance function of the splanchnic vasculature, impaired abdominal lymph flow can all be involved in subsequent deterioration of GFR. Additionally, dysfunction of congested abdominal organs, impaired intestinal barrier function, and endocrine effects of gut derived hormones or toxins further drive GFR decline.[25–27] Finally, aggressive decongestive therapy might result in intravascular underfilling, resulting in a drop in GFR.[17,18]

Proximal tubule

The major site of Na^+ reabsorption in the nephron is the proximal tubule. The reabsorbed fraction of filtered Na^+ (65%) is kept stable (65%) in the proximal tubule due to glomerulotubular feedback.[28] Several transporters on the luminal tubular membrane mediate Na^+ uptake. Subsequently, Na^+ is pumped out into the renal interstitium by Na^+/K^+-ATPases at the basolateral membrane. Peritubular capillaries reabsorb interstitial Na^+ while water passively follows in an iso-osmotic process.[29] Importantly, these Starling forces across the peritubular capillaries are not influenced by neurohumoral activation but determined by local haemodynamics of the microcirculation. Additionally, increased flow in the proximal tubule stimulates Na^+ reabsorption.

In HF, haemodynamic and neurohumoral changes facilitate Na^+ and water reabsorption in the proximal tubules (*Figure 3*). First, increased filtration fraction, as a result of reduced RBF, raises peritubular capillary oncotic pressure promoting Na^+ reabsorption. Second, renal venous hypertension substantially alters the hydrostatic pressure in both the renal interstitium and peritubular capillaries but also in the tubular lumen, since the kidney is an encapsulated organ.[30] Additionally, HF is characterized by an increased renal lymph flow, washing out interstitial proteins and decreasing colloid osmotic pressure in the renal interstitium, further promoting sodium reabsorption.[31,32] Peritubular capillaries are virtually impermeable to plasma proteins, which explains why intra-capillary colloidal osmotic pressure remains high.[29] To conclude, in HF, the amount of Na^+ delivered to the distal parts of the nephron will be substantially reduced, even more in case of a reduced GFR, which has important therapeutic implications as these are the sites of action for loop and thiazide type diuretics, as well as endogenous natriuretic peptides.

The loop of Henle

Only about a third of the volume filtered by the glomerulus reaches the loop of Henle. The loop of Henle plays a key role in both dilution and concentration of urine. The main functions of the loop are to remove more NaCl than water from the tubular fluid and to deposit this NaCl in the interstitium of the renal medulla, which provides the hypertonic gradient needed in the the distal parts of the nephron as a force to concentrate the urine (*Figure 4*).

Overall, the loop of Henle reabsorbs more salt than water, so the fluid entering the distal tubules will be hypo-osmotic. Whether the final urine is diluted or concentrated depends on how much water is reabsorbed by the distal nephron. This requires water permeability of these segments achieved by AVP and expression of aquaporin-2 channels (See supplementary material for a detailed description of normal physiology of the loop of Henle).[33,34]

In heart failure, natriuresis and maximal free water excretion are compromised (*Figure 5*). First, reabsorption of water and solutes is increased in the proximal tubules in heart failure, so less tubular fluid will be provided to the loop of Henle. Second, neurohumoral activation further increases active Na^+ reabsorption in the ascending parts of the loop of Henle.[35] Third, poor flow through the vasa recta as a result of vasoconstriction and poor renal blood flow prevents washout of solutes from the renal medulla impairing the capacity of the kidneys to dilute the urine and excrete free water.[36,37]

Loop diuretics increase the amount of tubular fluid presented to the distal nephron by their powerful inhibitory effect on $Na^+/K^+/2Cl^-$-symporters in the thick ascending limb of Henle's loop. Consequently, they interfere with the generation of hypertonicity in

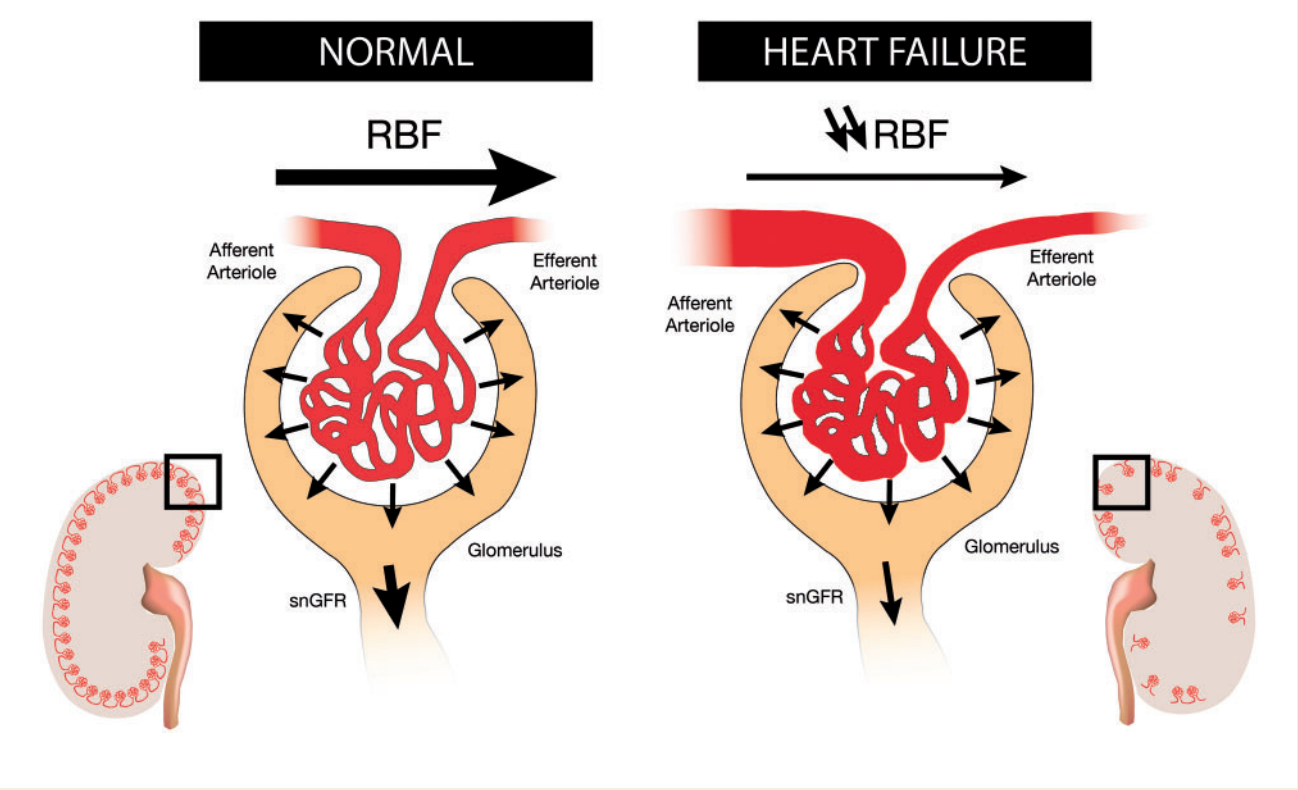

Figure 2 The glomerulus. Heart failure patients have an impaired GFR, lower renal blood flow with resulting increased filtration fraction, and increased renal vascular resistance in the efferent arteriole. RBF, renal blood flow; snGFR, single-nephron glomerular filtration rate.

the renal medullary interstitium, decreasing the osmotic gradient that is promoting water reabsorption in the collecting ducts. Because of the interference of loop diuretics with the renal capacity to concentrate urine, less free water is reabsorbed, resulting in production of hypotonic urine.[38]

Macula densa

The final part of the thick ascending loop of Henle contains packed cells in close to the afferent arteriole which secrete different hormones in response to changes in intra-tubular Cl^- concentrations (i.e. tubuloglomerular feedback) (*Figure 5*). After luminal transport by the $Na^+/K^+/2Cl^-$-symporter, a decrease in intracellular Cl^- concentrations initiates intracellular cyclo-oxygenase-2 and nitric oxide synthetase I activity, leading to paracrine prostaglandin E_2 and nitric oxide secretion. These paracrine signals decrease afferent arteriolar resistance, and thus increase intraglomerular hydrostatic pressure, RBF and GFR.[39] Furthermore, decreased Cl^- load will trigger renin release by afferent arteriolar cells, leading to further activation of the renin-angiotensin-aldosterone axis. High angiotensin II levels facilitate catecholamine release by the sympathetic nerve system, increasing vasoconstriction of predominantly the efferent arterioles and release of AVP in the posterior pituitary gland. Angiotensin II, increased sympathetic nerve activity as well as AVP promote the expression of active Na^+ transporters along the entire length of the nephron, thereby further promoting fractional Na^+ reabsorption.

As HF is characterized by an increased fractional Na^+ and Cl^- reabsorption in the proximal tubules, Cl^- delivery to the macula densa will further be reduced, which triggers through the aforementioned mechanism Na^+ reabsorption and neurohumoral activation, probably contributing to disease progression.[24] Importantly, loop diuretics 'deceive' macula densa cells by inhibiting Cl^- uptake which will directly trigger further renin release.

Distal convoluted tubule and collecting duct

The distal tubules reabsorb only a minor fraction (≤10%) of the total amount of Na^+ filtered by the glomerulus. However, they are very important as the distal fractional reabsorption rate varies significantly depending on the tubular flow rate, aldosterone and AVP levels.[40–42] Therefore, the distal convoluted tubule and collecting duct are responsible for fine-tuning the urinary Na^+ concentration and osmolality. However, maintaining a neutral Na^+ balance depends highly on adequate Na^+ delivery to the distal nephron.

Urinary dilution (i.e. free water excretion) is achieved through continued solute reabsorption, primarily through the thiazide-sensitive Na^+/Cl symporter and aldosterone-sensitive epithelial Na^+ channels.[43,44] The relatively low permeability of this segment to water is only overcome by insertion of aquaporin channels expressed when AVP is high (*Figure 6*).

In HF, tubular flow in the distal part of the nephron may be low despite significant volume overload secondary to increased fractional

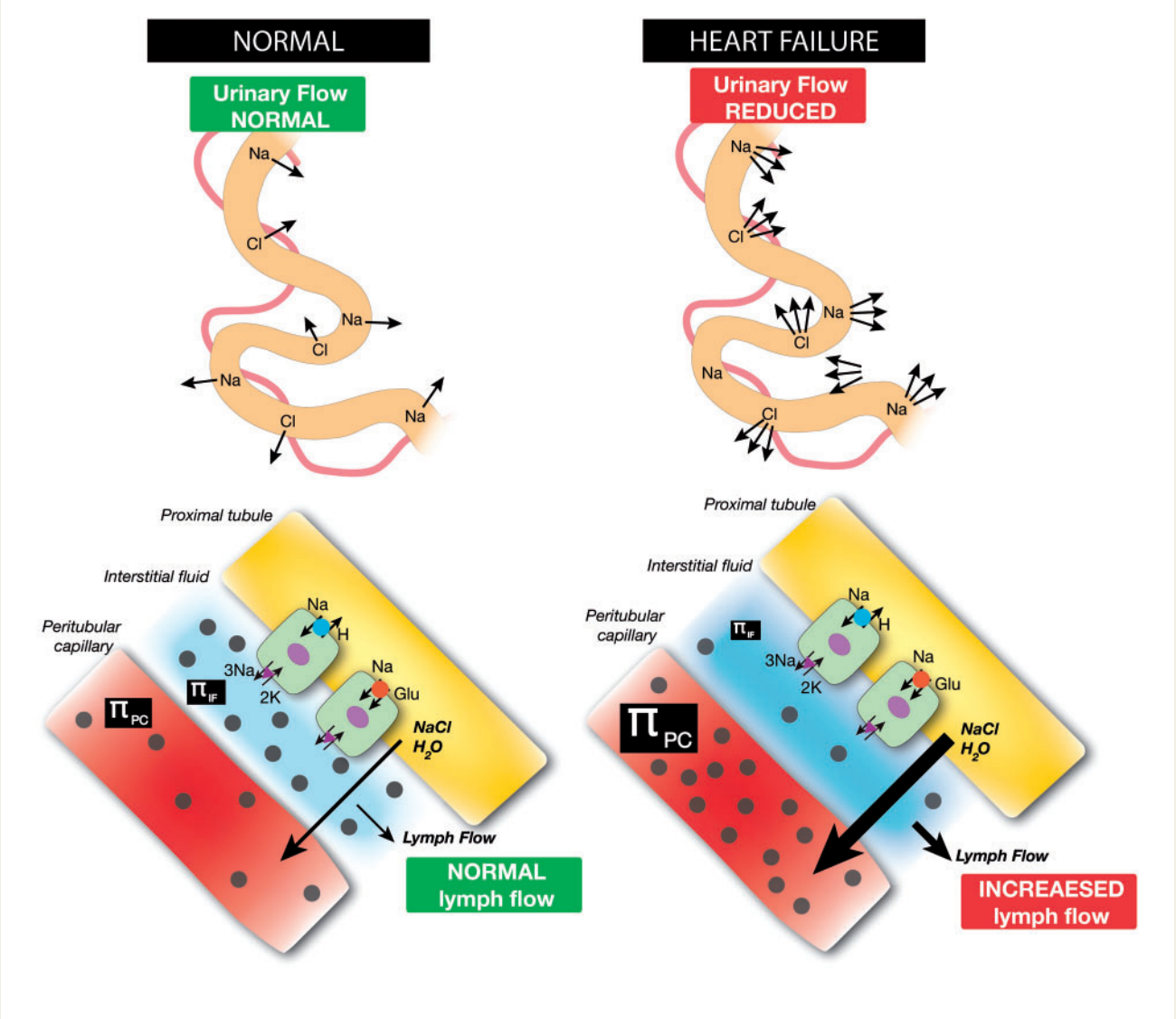

Figure 3 The proximal tubules. Haemodynamic and neurohumoral-induced changes in hydrostatic and colloid osmotic pressure in the renal interstitium and peritubullar capillaries facilitate Na^+ and water reabsorption in the proximal tubules. Additionally, an increased renal lymph flow washes out interstitial proteins and decreases colloid osmotic pressure in the renal interstitium further promoting passive Na^+ reabsorption. The absolute amount of Na^+ delivered to the distal parts of the nephron will be substantially reduced.

reabsorption in the proximal parts of the tubules and often concomitantly decreased GFR. Moreover, aldosterone levels are high, which further stimulates reabsorption of remaining tubular Na^+. Also, the presence of a high osmotic interstitial oncotic pressure (resulting from high Na^+ reabsorption more proximal, and low flow through vasa recta along the Loop of Henle) as well as high AVP levels further promote water retention.[45]

Finally, in HF, 'aldosterone break-through' and 'the braking phenomenon' often occur. In normal circumstances, large amounts of exogenous aldosterone do not cause oedema, since urinary Na^+ excretion exceeds aldosterone induced distal Na^+ reabsorption.[46] Aldosterone break-through occurs as the distal nephron cannot fully reabsorb the increased Na^+ load resulting from increased filtration due to volume expansion and upregulation of natriuretic peptides. However, in HF fractional Na^+ reabsorption in the proximal tubules is greatly enhanced, so distal Na^+ delivery remains low. As a result, aldosterone break-trough is observed despite treatment with an adequately dosed ACE-I.[47] Additionally, repeated dosing of loop diuretics leads to reduction in diuretic efficacy (= amount of Na^+ excreted per dose of loop diuretic), i.e. the so-called 'braking phenomenon' due to intrinsic renal adaptions with hypertrophy of distal tubular cells, causing increased distal Na^+ uptake as well as further aldosterone secretion.[48–51]

How to treat the increased renal sodium avidity in heart failure?

Treatment of renal sodium avidity is different in acute HF vs. chronic HF. Whereas in acute HF it is important to efficiently decongest the patient,

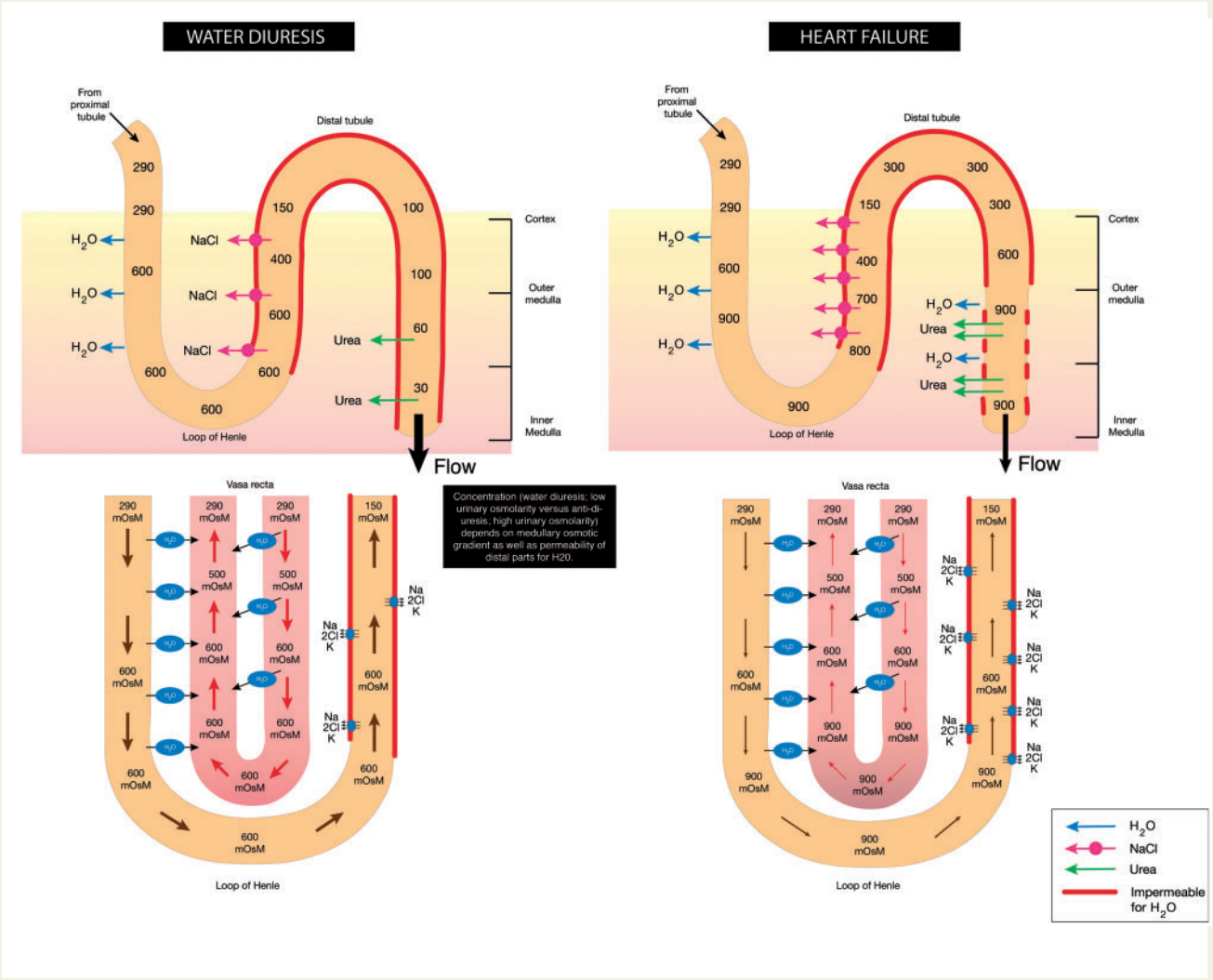

Figure 4 Loop of Henle and vasa recta. The hypertonic interstitium of the kidney increases in osmolality as the loop of Henle descends from the renal cortex towards the inner part of the medulla. The descending portion of the loop of Henle is extremely permeable to water. In contrast, the thick ascending part is impermeable to water, and luminal cells actively reabsorb solutes from the luminal fluid. The osmolality of the papilla can go up to 1200 mOsm because the hairpin loops of Henle and the vasa recta create a countercurrent flow mechanism that multiplies the single transverse gradient of 200 mOsm. The medullary facilitated urea transport in the collecting ducts is the other important factor to achieve hypertonicity of the renal interstitium. Vasa recta enter the medulla, lose water, and gain NaCl and urea progressively as they descend. When blood flow in the vasa recta capillaries reverses direction, water content increases again progressively as NaCl and urea are lost. In heart failure, less Na+ will be provided to the thick ascending limb of Henle's loop, impairing the ability of the kidney to concentrate and dilute urine.

in chronic HF the focus shifts to prevention of sodium and fluid accumulation through further uptitration of neurohumoral blockers (*Figure* 7).

Acute HF

Phenotypes

Haemodynamic congestion (i.e. increased cardiac filling pressures) does not equal volume overload (i.e. increased total body water, mainly in the extracellular compartment and manifesting as interstitial oedema, pulmonary oedema or pleural effusions, ascites, etc.).[52,53] Congestion without volume overload can often be efficiently treated by vasodilators, while volume overload should be addressed with diuretics or mechanical approaches of fluid removal. Independent of the used therapeutic strategy, hypotension during decongestive therapy should be avoided.[48,54–59]

Diuretics: adequately dosed, intravenously, and combination therapy

The most frequently applied therapy in acute HF to alleviate decongestion is loop diuretics. Importantly, persistent volume-overload is more consistently associated with worse outcome than short-term changes in GFR. However, the clinician often has to rely on the clinical examination, which lacks sensitivity, to evaluate the response to therapy. Guiding decongestive therapy by assessing natriuresis–which

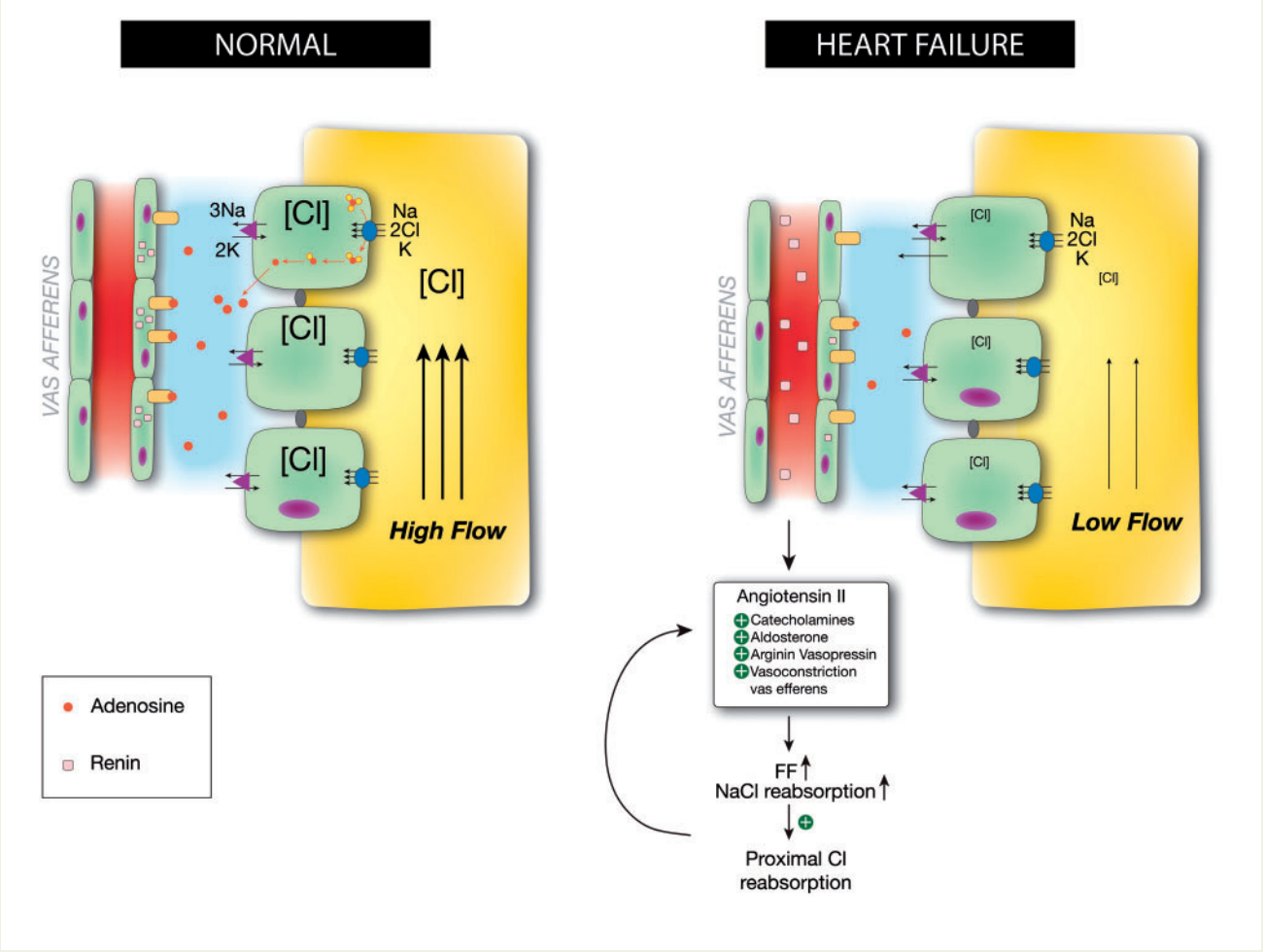

Figure 5 The macula densa. In heart failure, a decrease in Cl^- concentration inside macula dense cells, as a result of an increased fractional Na^+ and Cl^- reabsorption in the proximal tubules, triggers renin release, which results in increased vasoconstriction of predominantly the efferent arteriole, release of arginine vasopressin in the posterior pituitary gland and more active Na^+ reabsorption along the full length of the nephron.

reflects both glomerular and tubular function–might be a successful strategy to achieve effective decongestion.[2] Therefore, loop diuretic efficiency, defined as Na^+ output over loop diuretic dose, has emerged as one of the best markers to assess the cardio-renal interaction since this better reflects the renal reaction to volume status on the filtration and tubular level. Importantly, its prognostic strength is virtually unaffected even when adjusted for GFR.[48–50,56,58–60] However, logistic difficulties with collection of urine samples, and failure to identify the specific etiology and best treatment strategy, in case of a poor respons, e result in a lack of wide-spread clinical use at the moment. However, a urinary spot analysis after administration of a loop diuretic has been demonstrated to accurately reflect natriuretic response and might make an individualized approach in HF patients feasible.[61]

There are several reasons why loop diuretics might lose efficacy. First, loop diuretic efficacy depends on adequate delivery of the pharmacological agent itself and its substrate (i.e. NaCl) to the loop diuretic site of action at the luminal side of the thick ascending limb of Henle's loop. Importantly, loop diuretics must be actively secreted into the tubular lumen as they bind to the luminal surface of the transporter. This requires an adequate dosing strategy, with higher doses needed, especially if renal function is compromised.[62] Due to intra-abdominal oedema in acute decompensated HF, orally administered diuretics are less reabsorbed. Because of improved bioavailability of bumetanide and torsemide, they are preferred over furosemide in such cases.[63–65] However, IV diuretics are more effective. Based on the results of the Diuretic Optimization Strategies Evaluation (DOSE)-trial, no specific intravenous strategy (high vs. low, continuous vs. bolus) appeared to be superior over another.[66] In addition, concerns remain of potential adverse effects of high-dose loop diuretics on intravascular volume depletion with coinciding hypotension, neurohumoral activation (increased release of renin at macula densa level), potassium and magnesium wasting, and hyperuricemia.[67–69]

If adequately dosed IV loop diuretics are insufficient, combination therapy should be tried. Thiazide-type diuretics can overcome loop diuretic responsiveness caused by distal tubular hypertrophy.[70] Thus combining loop and thiazide diuretics

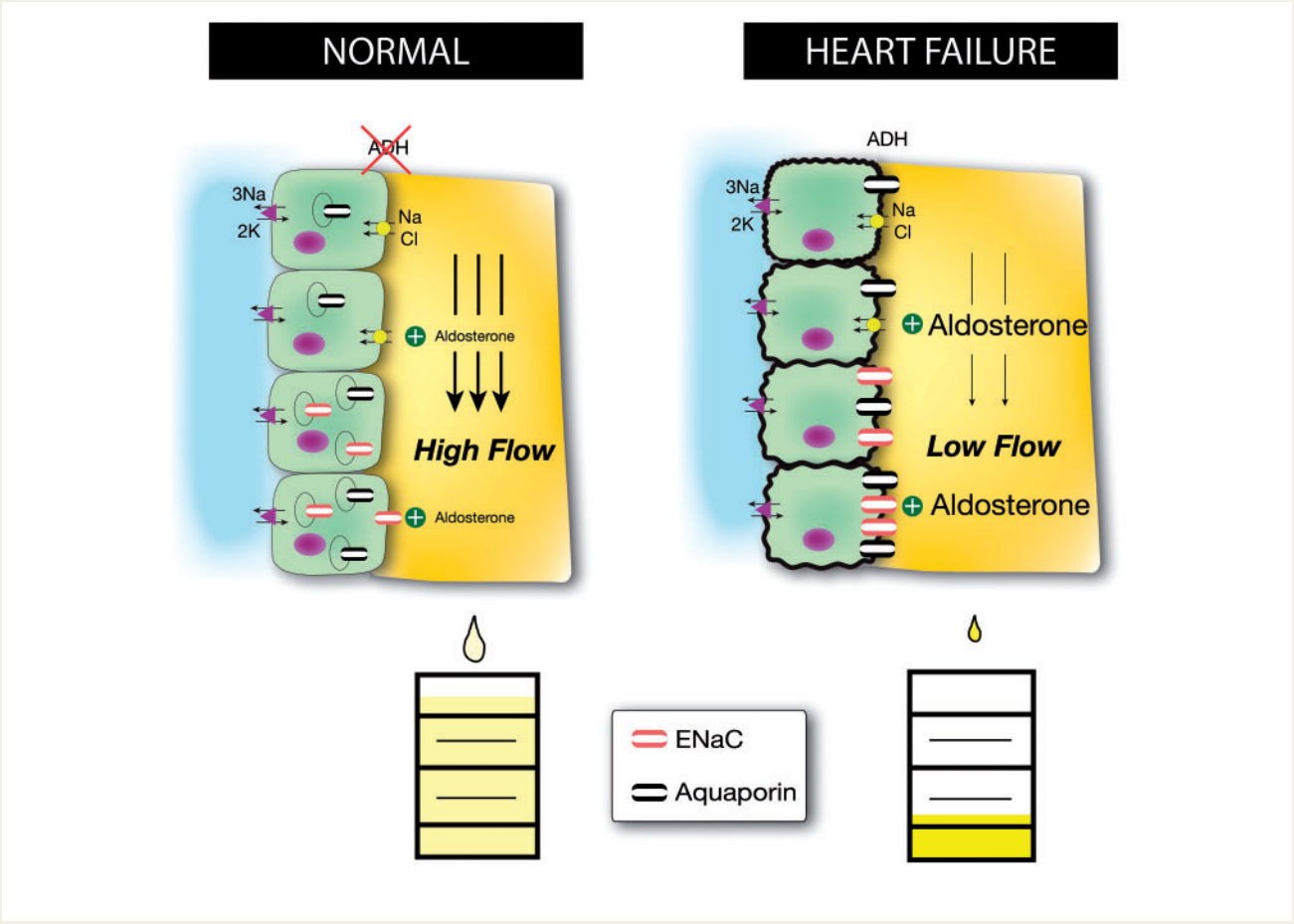

Figure 6 Distal convoluted tubules and collecting ducts. Distal fractional Na^+ reabsorption varies significantly depending on the tubular flow rate, and levels of aldosterone and arginine vasopressin (AVP). The relatively low permeability of this segment to water is only overcome by the insertion of aquaporin channels through AVP stimulation. In heart failure, tubular cells are often hypertrophic and flow in the distal part of the nephron is low. Moreover, aldosterone and AVP levels are high, stimulating reabsorption of tubular Na^+ and water.

seems appropriate in patients on chronic maintenance therapy with loop diuretics to increase the diuretic response. However, thiazide-type diuretics limit free water excretion and should be withheld in cases of hyponatremia.

Also, mineralocorticoid receptor antagonists have been an established treatment for symptomatic HF and counteract aldosterone break-through.[71,72] Additionally, to minimize potassium-wasting by loop diuretics and improve diuretic efficacy, there is a strong rationale to continue oral maintenance dosages of mineralocorticoid receptor antagonists and even increase the dose when GFR is stable and serum potassium levels are <5.5 mmol/L. However, the recently presented Aldosterone Targeted NeuroHormonal CombinEd with Natriuresis TherApy–Heart Failure (ATHENA-HF) trial did not demonstrate a more profound reduction in NT-proNP levels when high dose (100 mg daily) spironolactone was used during the first days of acute HF compared to continuation of low dose (25 mg daily) or placebo. Nevertheless, the investigators concluded that the role of high dose mineralocorticoid receptor antagonist specifically targeted to patients resistant to loop diuretics needs to be further studied in a large randomized trial.

Furthermore, targeting Na^+ reabsorption in the proximal tubules has several potential benefits in decompensated HF as it is the place where most Na^+ is reabsorbed. Indeed, blocking NaCl reabsorption proximally will provide more flow to more distal parts of the nephron including macula densa cells. This should be accompanied by decreased renin release and increased loop-diuretic efficacy. Such an approach is therefore especially warranted in cases of low RBF and low fractional Na^+ excretion. Acetazolamide, an old and largely forgotten diuretic which is hardly used in HF at the moment, is a carbonic anhydrase inhibitor which blocks sodium bicarbonate reabsorption in the proximal tubules.[24] One observational study in patients with acute HF and marked volume overload found that the addition of acetazolamide improved loop diuretic efficacy with ~100 mmol Na^+ excreted per 40 mg of furosemide-equivalent dose.[48] Furthermore, acetazolamide also improves thiazide-type diuretic efficacy, as it potently downregulates pendrin expression in the distal nephron.[73] Pendrin, also known as the sodium-independent Cl^-/iodide transporter, can compensate for Na^+ and Cl^- loss in the distal convoluted tubules and might be an unrecognized source of

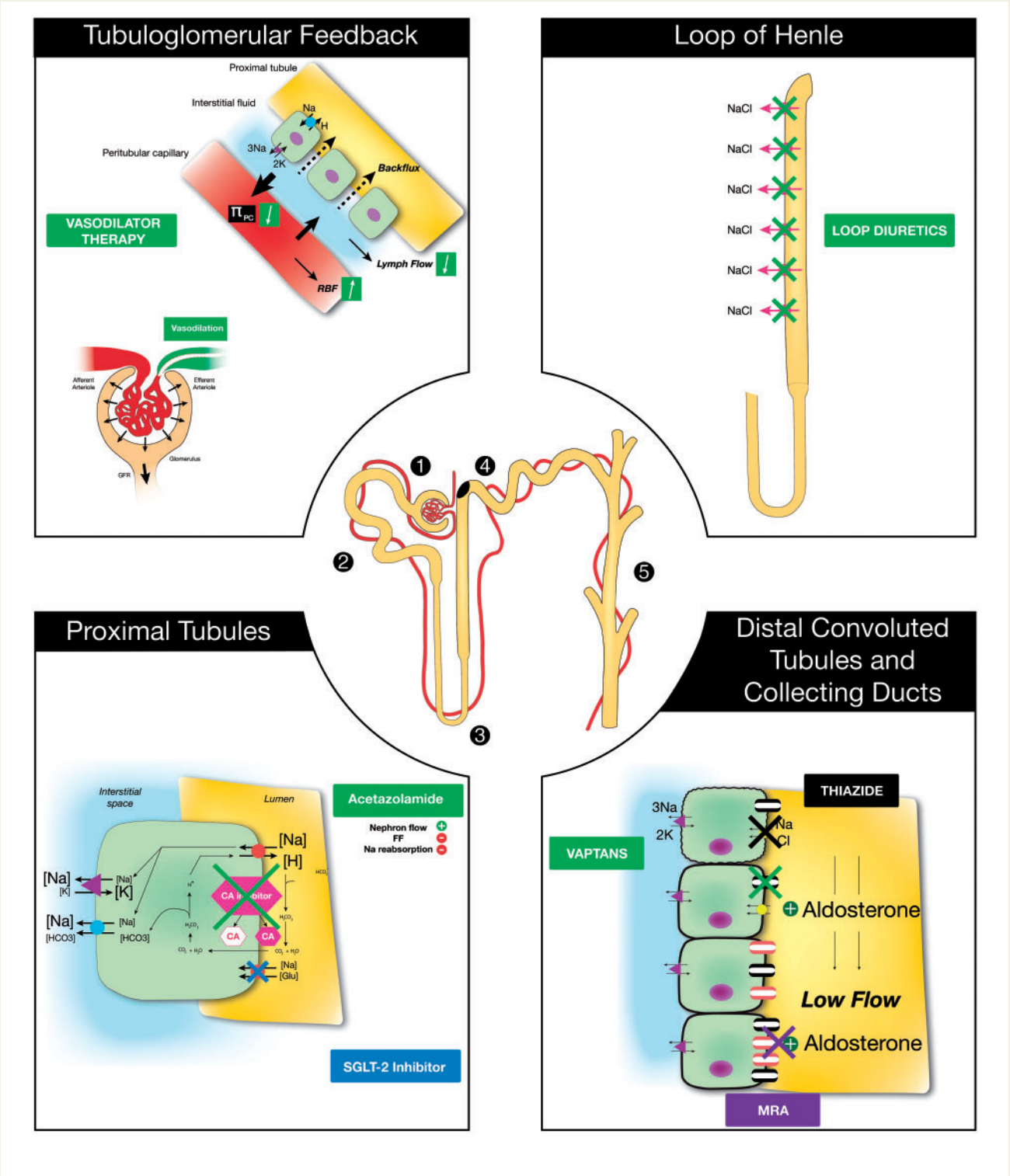

Figure 7 Different nephron segments with nephron-based therapy. *(A)* Vasodilation increases renal blood flow thereby lowering filtration fraction and reducing proximal sodium reabsorption. *(B)* Proximal-working diuretic agents (acetazolamide, sodium-glucose transporter-2 inhibitors) block proximal sodium reabsorption, promoting tubular flow and solvent drag resulting in more effective loop diuretic therapy and reduced renin release. *(C)* Loop diuretics block NaCl reabsorption in the loop of Henle and macula densa cells thereby reducing the medullar interstitial hypertonic gradient promoting both natriuresis and water excretion. *(D)* Thiazide-type diuretics block Na^+/Cl^- symporters in the distal convoluted tubules. *(E)* Mineralocorticoid receptor antagonists compete with aldosterone for binding to intracellular receptors causing: (1) decreased synthesis of apical Na channels (2) decreased Na/K ATPase pumps in the basolateral membrane. *(F)* Vaptans block aquaporin channels. (1) Glomerulus, (2) Proximal tubules, (3) Loop of Henle, (4) Macula densa, (5) Distal convoluted tubules and collecting ducts.

diuretic resistance.[74,75] Thus, although the diuretic and natriuretic capacity of acetazolamide is poor on its own, it might well be a very efficient booster of diuretic efficacy in combinational diuretic therapy with loop diuretics.[73,76] This concept is further supported by one small randomized trial including 24 patients with volume overload refractory to loop diuretic therapy.[77] All these patients demonstrated a greatly reduced fractional sodium excretion, which was easily overcome by the addition of acetazolamide. Whether improved diuretic efficacy with acetazolamide in heart failure and cardio-renal syndrome translates into better natriuresis and clinical outcomes is currently being tested in one randomized clinical trial (Clinical Trial NCT01973335).

Vasodilator therapy

Vasodilation in acute HF reduces cardiac afterload, increases renal blood flow and improves intrarenal haemodynamics. It also targets the principal haemodynamic problem in HF patients with high filling pressures but without clinical signs of volume overload. Also, in volume overloaded patients with acute HF, combination with vasodilator and diuretic therapy can facilitate decongestion. Vasodilator use is supported by a retrospective analysis of 4953 patients, which used propensity-matching to demonstrate improved survival over patients in whom cardiac output was increased through inotropes.[78] Additionally, another observational study has suggested that a lower dose of diuretics is needed to achieve decongestion when vasodilator therapy is added.[79] Observational data have demonstrated that nitroprusside titrated to blood pressure, with subsequent conversion to combinational treatment with oral hydralazine and nitrates is feasible, and potentially associated with better outcome in advanced HF with low cardiac output.[80,81] This approach is particularly attractive in patients in whom renin-angiotensin system blockers are contraindicated due to chronic kidney disease with severely compromised GFR.

However, low-dose dopamine or nesiritide, both sharing renal vasodilator properties, in participants with acute heart failure and renal dysfunction, did not enhance decongestion or improve GFR when added to standard diuretic therapy.[82] Furthermore, there was no significant difference between placebo and these therapeutics regarding re-hospitalization and death. Very recently, the Efficacy and safety of Ularitide for the treatment of Acute decompensated Heart Failure (TRUE-AHF trial) tested the hypothesis that Ularitide improves symptom relief, decongestion and kidney function in patients with acute HF. Ularitide, a chemically synthesized form of urodilatin, a human natriuretic peptide, is a novel drug also acting on the natriuretic pathway produced by differential processing of pro-atrial natriuretic peptide.[83] Phase I and phase II studies were promising.[84–87] However, the TRUE-AHF trial only demonstrated an advantage of Ularitide over placebo regarding short-term decongestion parameters and in-hospital heart failure events. Early vasodilator therapy with Ularitide could not reduce myocardial injury or long-term risk of cardiovascular death in this study. In contrast, in the Relaxin in Acute Heart Failure (RELAX-AHF) trial, serelaxin has emerged as the first therapy which potentially reduced all-cause mortality in patients with acute HF.[88] Serelaxin is recombinant human relaxin-2, which is normally produced by women during pregnancy. It potentially increases RBF and reduces filtration fraction but does not significantly affect the GFR.[89] Interestingly, the increase in RBF (up to 50%) probably relates to a reduction in venous congestion and vasodilation of the afferent and efferent arteriole unloading the glomerulus.[90] It remains to be proven in the ongoing RELAX-AHF-2 trial (Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF) that serelaxin offers more benefits than nesiritide/dopamine/ularitide regarding its predefined end-point.

Ultrafiltration

Studies on mechanical removal of fluid have yielded conflicting results.[91–93] Ultrafiltration removes isotonic fluid directly from the plasma compartment and is more efficient than diuretic therapy in getting rid of sodium. However, complications due to venous access and uncertainty about timing, patient selection, duration, and rate of fluid removal hamper its use.

Chronic HF

In chronic HF, preserving a euvolemic state through neurohumoral blockers and adherence to low sodium diet is critical to prevent HF disease progression. The need for loop diuretic use should be evaluated continuously, and the dose should be reduced if possible as they might prevent adequate uptitration of neurohumoral blockers. Intriguingly, new drugs in the treatment of chronic HF, which also decrease sodium avidity, have demonstrated improved HF hospitalizations and survival.

RAAS-blockers

Renin-angiotensin system blockers mediate *efferent* arteriolar vasodilatation and therefore an increase RBF while decreasing filtration fraction. Besides their impact on remodelling and prognosis in HF, RAAS-blockers lead to increased diuretic and natriuretic capacity in chronic (and acute HF), even in the face of a potential drop in GFR when therapy is initiated.[94]

SGLT-2 inhibitors

Sodium-glucose transporter-2 (SGLT-2) inhibitors–which recently demonstrated striking effects on cardiovascular endpoints in type II diabetes patients–induce an osmotic diuresis as well as direct inhibition of proximal tubular Na^+ absorption.[95] Therefore, like Acetazolamide, the SGLT-2 inhibitors are interesting options, yet to be studied in chronic HF, as they should enhance distal tubular flow in the nephron counteracting Na^+ retention, facilitating decongestive treatment, and boosting loop diuretic responsiveness.

Sacubitril/valsartan

Recent data demonstrated that sacubitril/valsartan–a combined angiotensin receptor blocker and neprilysin inhibitor–significantly reduces mortality among chronic HF patients with reduced ejection fraction compared to an ACE-I.[96] Based on these results, Sacubitril/Valsartan received a class IB recommendation in the 2016 European guidelines on Heart Failure to replace ACE-inhibition in ambulatory symptomatic HFREF patients. Data suggest that neprilysin inhibition provides beneficial outcomes by preventing the degradation of natriuretic peptides, and thereby promoting natriuresis, vasodilation and counteracting the negative cardiorenal effects of the upregulated RAAS.[97]

Conclusions

Heart failure is associated with increased Na^+ avidity and extracellular volume overload. Reduced number of nephrons, intra-renal haemodynamic alterations, neurohumoral activitation, and tubular hypertrophy all contribute to diminished natriuretic efficiency of diuretics. A tailored individualized use of combination diuretic therapy together with newly emerging treatment options, rather than blind uptitration of loop diuretics, could be beneficial to achieve thorough decongestion.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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