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Edema formation in congestive heart failure and the underlying mechanisms

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Congestive heart failure (HF) is a complex disease state characterized by impaired ventricular function and insufficient peripheral blood supply. The resultant reduced blood flow characterizing HF promotes activation of neurohormonal systems which leads to fluid retention, often exhibited as pulmonary congestion, peripheral edema, dyspnea, and fatigue. Despite intensive research, the exact mechanisms underlying edema formation in HF are poorly characterized. However, the unique relationship between the heart and the kidneys plays a central role in this phenomenon. Specifically, the interplay between the heart and the kidneys in HF involves multiple interdependent mechanisms, including hemodynamic alterations resulting in insufficient peripheral and renal perfusion which can lead to renal tubule hypoxia. Furthermore, HF is characterized by activation of neurohormonal factors including renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), endothelin-1 (ET-1), and anti-diuretic hormone (ADH) due to reduced cardiac output (CO) and renal perfusion. Persistent activation of these systems results in deleterious effects on both the kidneys and the heart, including sodium and water retention, vasoconstriction, increased central venous pressure (CVP), which is associated with renal venous hypertension/congestion along with increased intra-abdominal pressure (IAP). The latter was shown to reduce renal blood flow (RBF), leading to a decline in the glomerular filtration rate (GFR). Besides the activation of the above-mentioned vasoconstrictor/anti-natriuretic neurohormonal systems, HF is associated with exceptionally elevated levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). However, the supremacy of the deleterious neurohormonal systems over the beneficial natriuretic peptides (NP) in HF is evident by persistent sodium and water retention and cardiac remodeling. Many mechanisms have been suggested to explain this phenomenon which seems to be multifactorial and play a major role in the development of renal hyporesponsiveness to NPs and

cardiac remodeling. This review focuses on the mechanisms underlying the development of edema in HF with reduced ejection fraction and refers to the therapeutic maneuvers applied today to overcome abnormal salt/water balance characterizing HF.

Introduction

Generalized edema, the main clinical characteristic of extra cellular fluid (ECF) volume expansion, represents pathological sodium balance, and constant accumulation of water in excessive volumes in the interstitial compartment (1). It occurs in various edematous disease states including congestive heart failure (CHF), cirrhosis with ascites, and nephrotic syndrome. Regardless of its etiology, heart failure (HF) is primarily classified into two subgroups according to the ventricular ejection fraction (EF), namely HF with reduced EF (HFrEF) and HF with preserved EF (HFpEF). The prevalence of both HFrEF and HFpEF is roughly equal among HF patients, and both have a similar ominous prognosis, yet each subgroup exhibits unique clinical features and different responses to medical intervention (2, 3). HF is a clinical setting characterized by the incapability of the heart to perfuse enough blood and oxygen/nutrition to peripheral tissues. This happens frequently in low-output CHF. In response to these alterations, a series of compensatory circulatory and neurohormonal adjustments take place in order to maintain blood pressure and perfusion to various vital organs including the brain, lungs, and kidneys (4). In the early stages, these adaptations are beneficial and fulfill their compensatory role (compensated CHF). However, as CHF evolves, exaggerated stimulation of these systems becomes harmful as evident by profound systemic vasoconstriction and increased loading in the failing heart, eventually leading to the development of decompensated CHF (4, 5). Among the major abnormalities at the later stage is the disorder in the effector arm of volume control, where disproportionate activation of vasoconstrictor-sodium retaining systems, along with the failure of vasodilatory natriuretic factors, take place resulting in excessive salt and water balance (4, 5). Early and even before clinical cardiac failure manifestations develop, underlying renal aberrations limit their natriuretic response (6–9). This behavior agrees with the concept that the primary disturbance underlying sodium retention does not originate within the kidneys. Rather, renal sodium retention is secondary to circulatory disturbance provoked by the failing heart (10–12). The evolvement of the latter activates vasoconstrictive and anti-natriuretic systems that continue to retain sodium/water despite the subtle or overt expansion of ECF volume (13, 14).

The purpose of this review is to summarize the current understanding of the disturbances in the mechanisms that occur in one of the most widespread edema-forming states, namely CHF, and the derived therapeutic options applied today to overcome the elevated salt balance and edema characterizing this clinical setting.

Mechanisms underlying edema formation

Alterations in starling forces and interstitial fluid accumulation

Trans-capillary convective fluid flow and diffusive solute transport occur in CHF (1, 4, 15). The water movement is derived from hydrostatic and osmotic pressure gradients (5). Capillary hydraulic pressure is determined by several factors, such as arterial and venous blood pressures (SBP and CVP, respectively), blood flow, and resistances enacted by the pre- and post-capillary sphincters. While SBP is influenced by cardiac output (CO), systemic vascular resistance, and intra-vascular filling, systemic venous pressure is controlled by right atrial pressure, intra-vascular volume, and venous capacity. The latter hemodynamic parameters are profoundly dependent on sodium balance. Specifically, expansion of interstitial compartment can directly attenuate venous compliance and hence alter overall cardiovascular performance (16). Normally, the interstitial fluid pressure is sub-atmospheric, therefore, even a small increase in the volume of this ECF sub-space tends to enhance tissue hydraulic pressure, which opposes the movement of fluid into the interstitial compartment (17). Collectively, the development of generalized edema may stem from disorders in microcirculatory hemodynamics, where elevated venous pressure transmitted to the capillary is of major relevance to CHF as substantial renal fluid and sodium retention and increased ECF volume are hallmark features of this disease.

Perturbations of the afferent limb of volume homeostasis in congestive heart failure

The fact that the kidneys' ultrastructure is normal in CHF and keeps retaining sodium and water avidly, despite ECF expansion, may stem from either "backward failure" or "forward failure". The former indicates that the volume sensing mechanisms fail to appropriately detect the elevated circulating volume. According to this theory, the failing heart results in venous congestion along with increased capillary pressure, where both provoke fluid accumulation in the interstitium concomitantly to plasma volume depletion. Attenuation of plasma volume stimulates renal sodium and water retention. The concept of "forward failure" underscores the contribution of the myocardium failure in supplying sufficient blood to the various tissues including the kidneys, which are no longer able to maintain normal sodium excretion. Noteworthy, both theories emphasize the "underfilling of the arterial circulation", reduced cardiac output, and activation of neurohormonal responses (18–24). Therefore, a unifying hypothesis termed "arterial underfilling" was established to explain the sustained sodium and water retention by the kidneys in response to diminished cardiac output (10–12). In this context, hemodynamic alterations, and activation of neurohormonal compensatory systems in CHF, are similar to those seen in true dehydration. However, it should be emphasized that in contrast to real hypovolemia, CHF is characterized by elevated intracardiac pressures, which are supposed to stimulate the release of natriuretic peptides (NPs), namely atrial NP (ANP) and brain NP (BNP), and eventually provoke natriuretic and diuretic responses. The blunted natriuresis characterizing CHF may stem from interrupted signaling in afferent sensing sites localized to the cardiopulmonary system. These include disrupted baroreceptors located in the carotid sinus and aortic arch, besides malfunctioning of mechanosensitive nerve endings localized in cardiac chambers and cardiopulmonary system. Both arterial baro- and cardiopulmonary reflexes are blunted in CHF, as expressed by an inadequate tonic inhibitory effect on sympathetic outflow and eventually sympathetic nervous system (SNS) activation, together with anti-diuretic hormone (ADH) and renin secretion along promoting renal retention of salt and water despite of volume expansion (25, 26). In this context, it was shown that the interaction between volume sensing and urinary sodium excretion is maintained in compensated CHF (27), but not decompensated CHF, as was previously shown by Abassi et al. in an experimental model of heart failure induced by arteriovenous (A-V) fistula (13). Furthermore, important defects in the interaction between the cardiac and carotid baroreceptors and renal sympathetic activity have been reported in CHF. In this context, DiBona et al. (28) demonstrated a higher renal efferent sympathetic activity in rats with experimental CHF
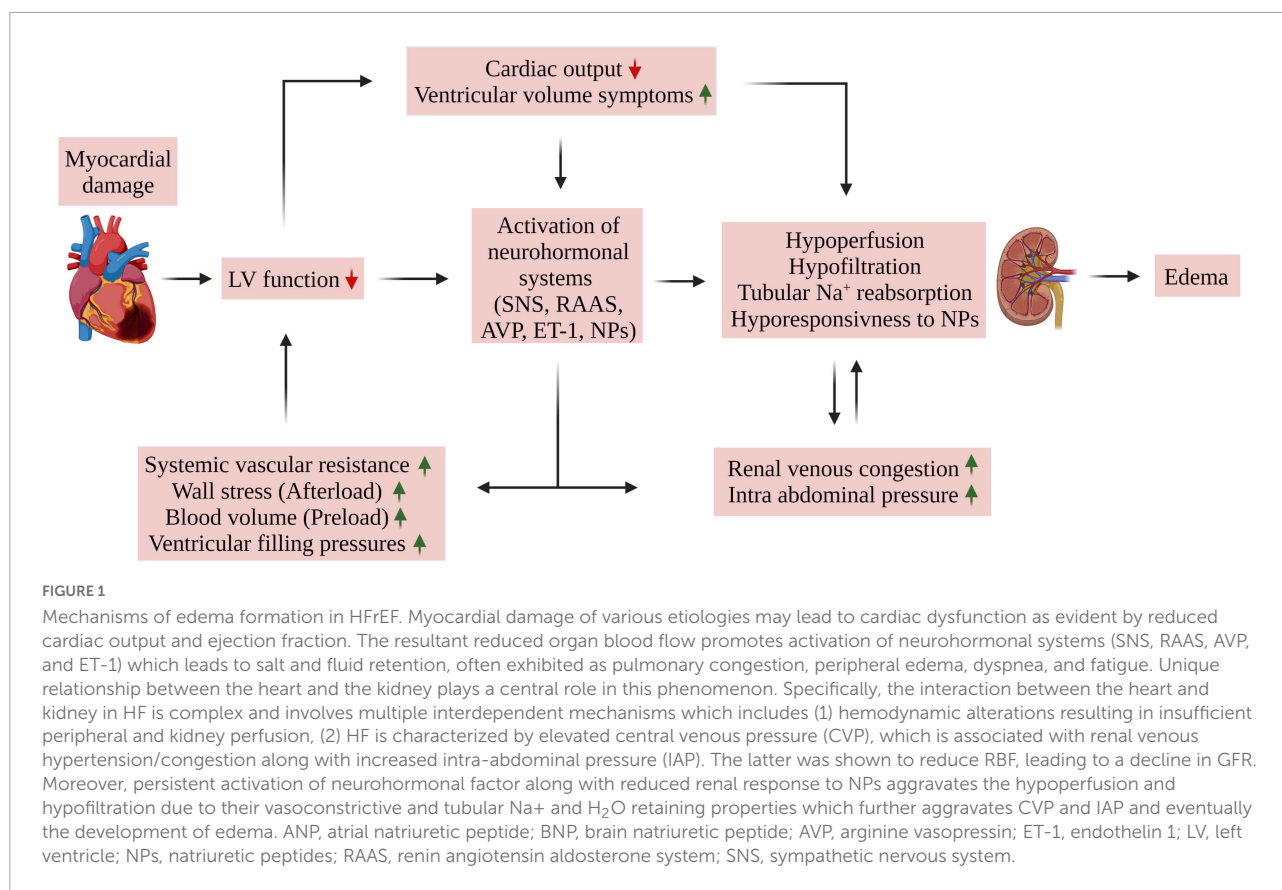
induced by left anterior descending (LAD) artery ligation. Interestingly, the renal sympathetic nerve hyperactivity of these animals was not attenuated following volume expansion. Moreover, the same group demonstrated that the aberrant regulation of renal sympathetic activity was associated with the disrupted function of cardiac, pulmonary, and arterial baroreceptors (29).

Abnormalities in efferent limb of volume homeostasis in congestive heart failure

Besides the aberrant sensing mechanisms, CHF is associated with the activation of several adaptive alterations in volume control. As mentioned above, these effector mechanisms include activation of neural, humoral, and paracrine systems that impose changes in glomerular hemodynamics and tubular transport, which in turn lead to avid sodium retention (1). On the other hand, CHF is also characterized by the activation of vasodilatory natriuretic systems, aimed at opposing the vasoconstrictor anti-natriuretic factors. Thus, the net effect on sodium and water balance in CHF is determined by the balance between these antagonistic systems. Although activation of these vasodilatory and natriuretic systems is essential to counterbalance the vasoconstrictor/antinatriuretic systems, abnormal and continuous activation of the efferent limb of volume control along blunted renal action of NPs profoundly contribute to the classic manifestations of CHF and further deterioration of cardiac function (1).

Alterations in glomerular hemodynamics

The interplay between the heart and kidneys in CHF is complex (**Figure 1**), involving multiple interdependent mechanisms, which can be divided into four categories (6–9): (1) Insufficient peripheral blood flow during HF results in deleterious alterations in renal hemodynamics as evident by increased renal vascular resistance, reduced glomerular filtration rate (GFR), and a marked reduction in renal plasma flow (RPF) resulting in increased filtration fraction (FF). This phenomenon was observed in rats with CHF induced by left coronary ligation (30), where CHF rats exhibited lower single nephron GFR (SNGFR) than control animals. Micropuncture assessment revealed a reduction in single nephron plasma flow (SNPF) which was to a greater extent than the decline in SNGFR, accounting for a higher single nephron filtration fraction (SNFF). The preferential decline in SNPF as compared with SNGFR is attributed to vasoconstriction of both afferent, and especially efferent arterioles. Similar alterations in glomerular hemodynamics have been also reported in rats with A-V fistula,

FIGURE 1

Mechanisms of edema formation in HFrEF. Myocardial damage of various etiologies may lead to cardiac dysfunction as evident by reduced cardiac output and ejection fraction. The resultant reduced organ blood flow promotes activation of neurohormonal systems (SNS, RAAS, AVP, and ET-1) which leads to salt and fluid retention, often exhibited as pulmonary congestion, peripheral edema, dyspnea, and fatigue. Unique relationship between the heart and the kidney plays a central role in this phenomenon. Specifically, the interaction between the heart and kidney in HF is complex and involves multiple interdependent mechanisms which includes (1) hemodynamic alterations resulting in insufficient peripheral and kidney perfusion, (2) HF is characterized by elevated central venous pressure (CVP), which is associated with renal venous hypertension/congestion along with increased intra-abdominal pressure (IAP). The latter was shown to reduce RBF, leading to a decline in GFR. Moreover, persistent activation of neurohormonal factor along with reduced renal response to NPs aggravates the hypoperfusion and hypofiltration due to their vasoconstrictive and tubular Na+ and H_2O retaining properties which further aggravates CVP and IAP and eventually the development of edema. ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; AVP, arginine vasopressin; ET-1, endothelin 1; LV, left ventricle; NPs, natriuretic peptides; RAAS, renin angiotensin aldosterone system; SNS, sympathetic nervous system.
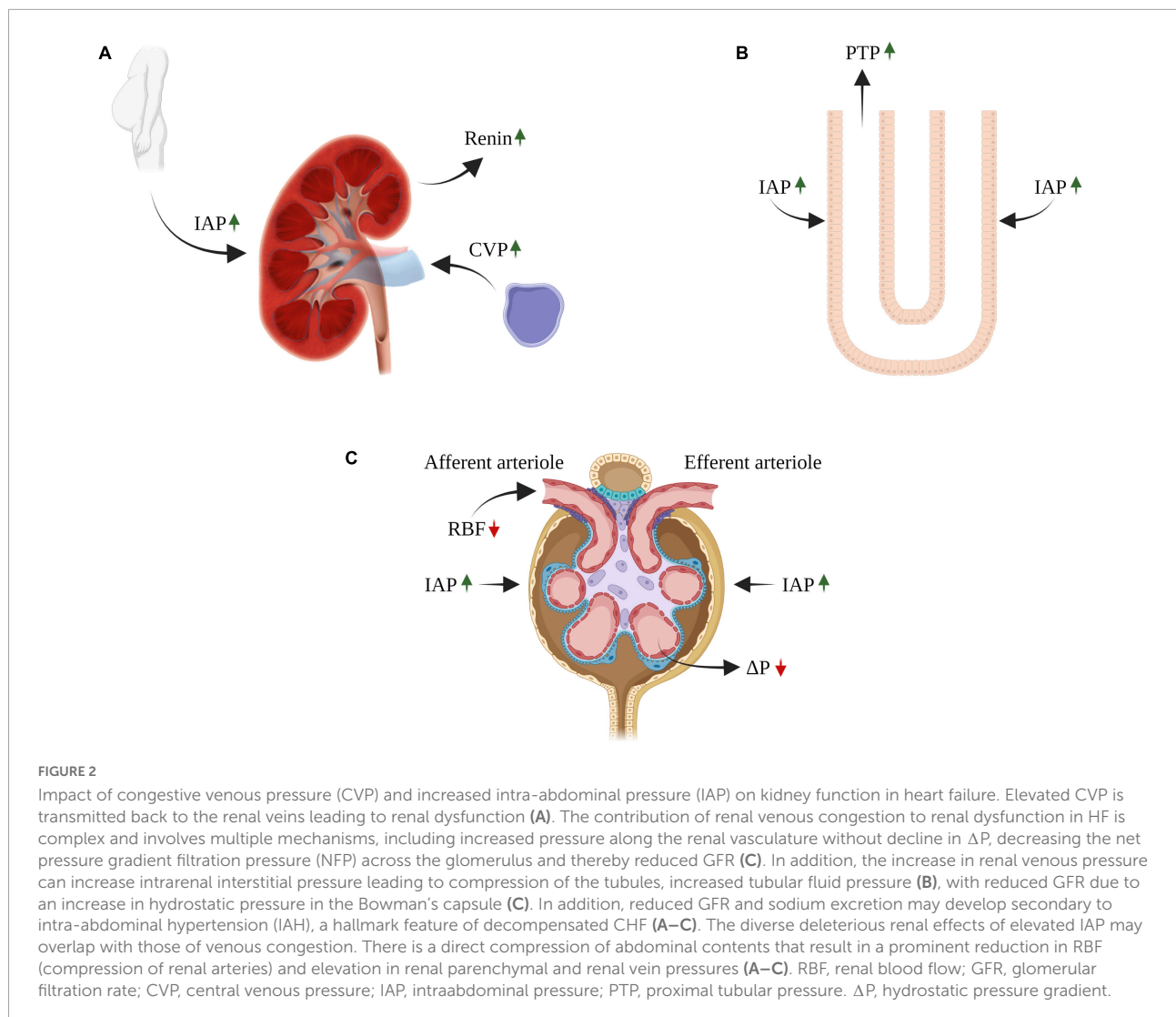
a high output failure model (31). As a result, colloid osmotic pressure gradient ($\Delta\pi$) enhances over the glomerular capillary which eventually leads to impaired GFR as the hydrostatic pressure gradient (ΔP) is decreased too. Since the kidneys receive about one-quarter of CO and considering that GFR is dependent on RPF, renal hypoperfusion can lead to renal hypoxia; (2) HF is characterized by elevated CVP, which is associated with renal venous hypertension (32). The latter was shown to reduce RBF in animal models, leading to a decline in GFR (4); (3) Activation of neurohormonal factors, where the reduced CO and the subsequent decline in blood pressure and renal perfusion activate the renin-angiotensin-aldosterone-system (RAAS) and SNS. Activation of these neurohormonal systems results in deleterious effects on both the kidneys and the heart, including sodium and water retention, systemic and renal vasoconstriction, elevated venous volume/return, and enhanced oxidative stress. Moreover, angiotensin II (Ang II) and aldosterone promote cardiac and renal remodeling (33, 34). In addition, HF is characterized by increased production of endothelin-1 (ET-1) and ADH following baroreceptor activation (7), both of which enhance systemic vasoconstriction and reduce free water clearance; (4) secretion of various factors that play an important role in the deterioration of the cardiac and renal function along with systemic and local inflammation, endothelial dysfunction, anemia, and other

metabolic alterations (6, 35). In summary, worsening renal function (WRF) during acute decompensated HF occurs mainly due to systemic hemodynamic derangements, such as increased venous pressure, elevated intra-abdominal pressure (IAP), and drop in arterial blood pressure along with diminished cardiac function (see the following sections).

Tubular sodium retention

The adverse alterations in glomerular hemodynamics, WRF, impaired tubular flow, and hormonal status characterizing decompensated CHF enhance tubular reabsorption of sodium at both the proximal nephron and collecting duct (4). As mentioned above, the elevated $\Delta\pi$ along the decreased ΔP through the glomerular capillary length favors fluid movement from the tubular lumen into the capillary, and sodium and water reabsorption in the proximal tubule to peritubular capillaries. Since the kidneys are encapsulated, renal venous congestion elevates the interstitial hydrostatic pressure in both the kidneys, peritubular capillaries, and tubuli (Figure 2) (36). Likewise, the enhanced renal lymphatic flow characterizing CHF reduces interstitial π, thus aggravating tubular salt reabsorption (37). The latter is manifested by avid proximal sodium reabsorption as a result of abnormal

FIGURE 2
Impact of congestive venous pressure (CVP) and increased intra-abdominal pressure (IAP) on kidney function in heart failure. Elevated CVP is transmitted back to the renal veins leading to renal dysfunction **(A)**. The contribution of renal venous congestion to renal dysfunction in HF is complex and involves multiple mechanisms, including increased pressure along the renal vasculature without decline in ΔP, decreasing the net pressure gradient filtration pressure (NFP) across the glomerulus and thereby reduced GFR **(C)**. In addition, the increase in renal venous pressure can increase intrarenal interstitial pressure leading to compression of the tubules, increased tubular fluid pressure **(B)**, with reduced GFR due to an increase in hydrostatic pressure in the Bowman's capsule **(C)**. In addition, reduced GFR and sodium excretion may develop secondary to intra-abdominal hypertension (IAH), a hallmark feature of decompensated CHF **(A–C)**. The diverse deleterious renal effects of elevated IAP may overlap with those of venous congestion. There is a direct compression of abdominal contents that result in a prominent reduction in RBF (compression of renal arteries) and elevation in renal parenchymal and renal vein pressures **(A–C)**. RBF, renal blood flow; GFR, glomerular filtration rate; CVP, central venous pressure; IAP, intraabdominal pressure; PTP, proximal tubular pressure. ΔP, hydrostatic pressure gradient.

glomerular hemodynamics and activation of neurohormonal systems as have been shown in both experimental and clinical studies (4, 38). Evidence for exaggerated proximal sodium reabsorption conjugated with low delivery of sodium to more distal tubuli during CHF induced by LAD ligation was derived from clearance experiments where mannitol was infused (30, 39), inhibition of distal sodium reabsorption (40) and deoxycorticosterone acetate (DOCA) escape (41). Further support for this notion came from the findings that restoring the increased SNFF with angiotensin-converting enzyme (ACE) inhibitor normalized proximal peritubular capillary starling forces and sodium reabsorption (41). Yet, direct actions of Ang II and norepinephrine (NE) secreted from the renal nerve contribute to the enhanced proximal sodium reabsorption (4). In this regard, both Ang II and NE may act by modulating both renal hemodynamics, as well as by directly boosting proximal sodium epithelial transport, thus augmenting the overall proximal sodium reabsorption capacity (4). Besides the

proximal tubule, the distal nephron site also takes part in the exaggerated tubular sodium reabsorption in experimental models of CHF. Specifically, applying micropuncture technique in experimental high or low CO CHF revealed enhanced distal nephron sodium reabsorption (42–45). Moreover, dogs with CHF induced by vena cava constriction cannot excrete sodium load due to exaggerated sodium reabsorption by loop of Henle (46). In this context, reduced medullary blood flow due to vasoconstriction prevents washout of solutes from the renal medulla, thus leading to reduced free water excretion and consequently to impaired urinary dilution (47).

Humoral mechanisms

Most hospitalized CHF patients display a variable degree of volume overload (48, 49). This is largely attributed to the mobilization of compensatory anti-natriuretic and

vasoconstrictive systems including RAAS, SNS, ADH, and endothelins (ETs), which enhance vascular resistance and promote salt and water reabsorption by the kidneys (4). These deleterious actions overcome the activated vasodilatory/natriuretic substances, such as NPs, nitric oxide (NO), prostaglandins (PGs), adrenomedullin (AM), and urotensin II (UII) (13). It is well accepted that salt and water balance is largely determined by a fine balance between these antagonistic systems, namely vasoconstrictive/anti-natriuretic and vasodilator/natriuretic substances. The development of excessive sodium balance and generalized edema in CHF represents a milestone where the balance is in favor of the vasoconstrictive/anti-natriuretic systems (**Figure 1**). However, up to 60% of HF patients suffer from a certain degree of kidney dysfunction (GFR < 60 ml/min), which reduces their ability to excrete excessive amounts of sodium (32). This subgroup of CHF patients became of special interest in the last few years, as numerous studies uncovered that kidney dysfunction in CHF is a stronger predictor of mortality than impaired cardiac performance (50–54). Collectively, these findings confirm that WRF is common in HF and has been associated with decreased survival, a high rate of hospitalization, and disease progression (53, 54).

Neurohormonal systems

Vasoconstrictive/anti-natriuretic systems
Renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system (RAAS) plays a critical role in the homeostasis of ECF volume, sodium balance, blood pressure, and cardiac performance (55, 56). This sodium/water-retaining and vasoconstrictive system is activated in hypovolemic and hypotensive conditions which compromise hemodynamic stability, such as hemorrhage, hypotension, dehydration, low sodium intake, and activation of SNS. Our understanding of the RAAS has been evolving over the last 120 years (57, 58). Classically, the RAAS is considered as a paracrine/endocrine axis involved in tubular sodium reabsorption and vasoconstriction, thus may eventually lead to the development of hypertension and target organ damage with concomitant inflammation, oxidative stress, cell proliferation, apoptosis, fibrosis, and coagulation (57, 59). The system cascade is initiated and regulated by the classic renin activity originating from the kidneys (Granular cells) (60), but also expressed locally in the heart during HF (61–64). Renin produces angiotensin (Ang) I, an inactive 10 amino acid (aa) peptide from circulating angiotensinogen. Ang I is then converted by ACE to Ang II, an 8 aa active peptide. ACE is primarily localized to the endothelial cells of the pulmonary vasculature. The deleterious impact of RAAS is attributed to its main component, namely Ang II, where it exerts its adverse actions by binding to angiotensin II receptor type 1

(AT1R) expressed in various target organs including the kidneys, heart, and blood vessels. The development of ACE inhibitors (ACEi), and later of AT1R blockers (ARBs), revolutionized the therapeutic approach to kidney and heart diseases (65–68), where both groups of RAAS blockers attenuate cardiac and renal remodeling and slow down the progression of HF (69–72) and chronic kidney disease (CKD) (73–75). Aldosterone, the other active component in the RAAS cascade, was also found to enhance sodium retention by the principle cells localized to the collecting duct, thus contributing to ECF expansion and independently accelerating organ fibrosis, a process revised by aldosterone antagonists (76).

However, the complexity of the RAAS has been unraveled in the last two decades, where numerous studies reported that besides the adverse ACE/Ang II/AT1R axis (the "pressor arm"), there is a beneficial and protective pathway that attenuates the adverse vasoconstrictory and salt-retaining effects of the abovementioned axis (the "depressor arm") (77, 78). Specifically, our attention was shifted to another component of the RAAS, namely angiotensin-converting enzyme 2 (ACE2). The latter converts Ang II to the bioactive 7-amino-acid peptide, Ang 1–7. Moreover, ACE2 converts Ang I into Ang 1–9, which can be further converted to Ang 1–7 by ACE. Additional pathway of Ang 1–7 production involves neural endopeptidase, or neprilysin (NEP), which converts Ang I directly into Ang 1–7 (79–84).

Ang II exerts its anti-diuretic and anti-natriuretic effects through the regulation of both renal hemodynamic and tubular sodium and water transport (55). Specifically, Ang II pressor action on the kidney decreases renal blood flow and urinary sodium excretion. In this context, Ang II binds to AT-1 receptors localized to renal vascular smooth muscle cells, causing vasoconstriction of both the afferent and efferent arterioles, resulting in kidney hypoperfusion. Moreover, activation of AT-1 receptors in the brain increases cardiac and vasculature sympathetic output, thus increasing CO and total peripheral resistance along elevated blood pressure. In addition, Ang II provokes ADH release from the posterior pituitary gland, which in turn enhances water retention by the collecting duct to maintain blood volume. Finally, Ang II stimulates thirst, where the increased water intake increases ECF including blood volume, which collectively raises blood pressure (55). The elevated circulatory levels of Ang II or local within-organ RAAS activation in HF (85) aggravates tubular handling of salt and water, by directly stimulating proximal tubular sodium absorption and indirectly *via* increasing the release of aldosterone and endothelin, and stimulating thirst despite a typically low serum osmolality (86). Therefore, blockade of the RAAS in HF patients with reduced ejection fraction (EF) by administration of either ACE inhibitors or ARBs can facilitate sodium excretion although can deteriorate renal hemodynamics and eventually kidney function due to efferent arteriole vasodilation (54, 87, 88). In this regard, a meta-analysis

of published study data by Beldhuis (89) on 28,961 patients revealed that RAAS inhibitors induce WRF in both HFrEF and HFpEF. The latter group exhibited an increased mortality risk when placed on RAAS inhibitors. In contrast, WRF in HFrEF following treatment with ACE inhibitors increased the mortality rate to a lesser extent as compared with HFpEF patients on RAAS inhibitor-induced WRF.

ACE2 is a transcellular protein, which is abundantly expressed in several vital organs, such as the intestine, kidney, endothelial cells, heart, lung, brain, and testis (80). In the heart, ACE2 is widely expressed in the endothelium, smooth muscle cells, and cardiac myocytes (90). As mentioned above, locally expressed ACE2 converts Ang II to Ang 1–7 (81), which exerts vasodilatory, natriuretic/diuretic, anti-inflammatory, and anti-fibrotic effects *via* Mas receptor (MasR) (84). Notably, both clinical and experimental HF displays upregulation of cardiac ACE2 and enhanced Ang 1–7 production, which may represent a cardioprotective compensatory mechanism aimed at counterbalancing the adverse effects of ACE/Ang II/AT1R axis on the myocardium (84, 90, 91). In this context, Tripathi et al. have demonstrated that ACE2/Ang 1–7/MasR exerts a protective role toward systemic and pleural edema suppression along with enhanced survival in mice model of HFrEF with progressive dilated cardiomyopathy (DCM), without comorbidities from modulated blood pressure and renal failure (92).

In summary, Ang II, the main effector of the RAAS, controls ECF and urinary sodium excretion *via* renal hemodynamic and tubular actions, along with systemic vasoconstriction, as well as aldosterone and ADH release mechanisms. The intra- and extra-renal actions of Ang II are exaggerated under a variety of disease states, such as HF, thus aggravating cardiac dysfunction and myocardial remodeling. The presence of ACE2/Ang 1–7/MasR may act as a protective arm to face the deleterious arm of the RAAS, namely, ACE/Ang II/AT1-R axis.

Sympathetic nervous system

Renal sympathetic nerves innervate the vasculature and nephrons, where they play a central role in the regulation of renal hemodynamics and tubular function (93, 94). Specifically, sympathetic nerve endings were observed in smooth muscle cells of renal vessels, mesangial cells, juxtaglomerular granular cells, and the various tubular segments, including proximal convoluted, Henle's loop, and distal tubuli. The early stages of HF are characterized by high sympathetic activity and high levels of circulatory NE, which harmfully affect vital organs, including the heart and kidneys (95). As mentioned above, the activation of neurohormonal systems during HF is initially beneficial in maintaining systemic blood pressure (BP) and adequate organ perfusion, however, it becomes detrimental as the disease evolves (96). Increased renal sympathetic nerve outflow attenuates urinary sodium and water excretion through (1)

exaggerated tubular sodium reabsorption throughout the nephron; (2) hypoperfusion and hypofiltration by inducing afferent and efferent arteriole vasoconstriction; and (3) provoking renin secretion from the juxtaglomerular granular cells (**Figure** 2), which eventually leads to RAAS activation (60) and attenuation of the renal actions of ANP (97). Support for the major contribution of the renal nerve to renal excretory and hemodynamic derangement was derived from experimental HF studies showing decreased sodium retention, hyperperfusion, hyperfiltration, and vasodilation of both afferent and efferent arterioles following renal denervation (95, 97, 98). In line with these findings, α or β receptors antagonists also enhanced urinary excretion of sodium and water, probably secondary to improvement in both renal and cardiac hemodynamics and suppression of renal sympathetic nerve, as well as RAAS activity (1, 99), although this matter remains somewhat controversial (100). Collectively, activation of the renal sympathetic nerve composes a major factor in the anti-natriuretic and vasoconstrictive systems which largely contributes to avid renal sodium and water retention characterizing patients with advanced HF (101).

Anti-diuretic hormone

Since the pioneer report by Szatalovicz et al. in the early 80s (102), several studies have reported elevated circulatory levels of ADH in patients with HF, especially in those with advanced CHF and hyponatremia (1). The increased secretion of ADH in these patients is attributed to non-osmotic stimuli such as attenuated compliance of the left atrium and activation of the baroreceptors and RAAS (101, 103). This non-osmotic release of ADH is largely responsible for hyponatremia, a clinically important complication of heart failure, as ADH stimulates V2 receptors (V2) along increased aquaporin-2 AQP-2 water channel density in the apical side of epithelial cells in the collecting duct, ensuing water retention and eventually hyponatremia. The contribution of ADH to the excessive water balance in CHF is supported by the findings that oral treatment with V2 antagonists (Aquaretics) provoked significant free water clearance, low urinary osmolarity, and elevation of plasma osmolality, along with downregulation of AQP-2 in the collecting duct (104). Besides the activation of the V2/AQP-2, ADH also stimulates V1a receptors localized to the vascular smooth muscle cells, with constriction of coronary vessels and stimulation of cardiac myocyte proliferation (101, 103). These findings suggest an adverse role for vasopressin in fluid overload and cardiac remodeling characterizing CHF patients. This notion is supported by clinical trials demonstrating that V2 blockade induces diuresis and lowers congestion without WRF when administered with furosemide to chronic HFrEF, but unfortunately did not improve outcomes when applied during the post-acute phase (105). In summary, these results implicate ADH in the pathogenesis of water retention and hyponatremia

characterizing CHF, and that V2 receptor blockade may bear potential therapeutic properties for clinical CHF.

Endothelin

The endothelin family contains three members, namely endothelin-1 (ET-1), the most famous representative, endothelin-2 (ET-2), and endothelin-3 (ET-3). These peptides are generated and secreted mainly by endothelial cells, and act in the proximity of their production in a paracrine/autocrine mode of action *via* endothelin receptors A and B (ETA and ETB, respectively). Besides their explicit role in normal physiology, ETs are involved in the pathogenesis of many diseases, including cardiovascular and renal disorders (106, 107). Under normal conditions, ET-1 regulates basal vascular tone, glomerular hemodynamics, and sodium homeostasis. At the cardiac level, ET-1 synthesis takes place in cardiac myocytes, where it exerts positive inotropic effects at low doses, but can cause a reduction in CO at high concentrations. In addition, numerous studies have demonstrated that the kidney is a major site of ET-1 synthesis (mainly the inner medulla), besides being a preferential target organ of this peptide. Specifically, ET-1 exerts various effects on the kidneys, where it affects renal function by modulating: (1) renal vascular resistance; (2) tubular salt and water reabsorption; and (3) tonus, proliferation, and mitogenesis of mesangial cells (106). Noteworthy, this system is also involved in various pathophysiological conditions including hypertension, myocardial hypertrophy, and inflammation, and in the development and progression of renal and cardiovascular diseases, including CKD and CHF (108). Concerning the latter, ET-1 plays a role in cardiac remodeling *via* increasing fibroblast activation and inflammation in the failing heart or secondary to RAAS activation (108). Furthermore, the endothelin system is involved in kidney dysfunction in both acute and chronic kidney failure by inducing deleterious actions such as oxidative stress, inflammation, renal remodeling, interstitial fibrosis, glomerulosclerosis, reduced RBF and GFR, and water and sodium retention (109, 110). It should be emphasized that CKD and persistent congestion influence HF prognosis as was demonstrated in patients hospitalized with acute HF (111). Interestingly, the prognostic impact of these two parameters is associated with increased cytokine levels, suggesting an adverse role of inflammation in the prognostic impact of congestion and CKD and may also interfere with the outcome of these patients (111).

The pathophysiological involvement of ET-1 in CHF is supported by a few observations: (1) several studies have documented upregulation of the ET system in CHF (112). (2) Both experimental and clinical studies have reported that ET-1 receptor antagonists improved the severity of this disease state. Considering that CHF is associated with reduced renal perfusion along increased vascular resistance and elevated levels of ET-1, it is tempting to suggest a cause-and-effect relationship between the adverse alteration in renal hemodynamics and the activation of ET-1 in this clinical setting. Indeed, experimental studies have shown that administration of bosentan, a mixed ETA/ETB receptor antagonist, into rats with severe decompensated CHF induced by placement of aortocaval fistula remarkably improved RBF, as was evident by enhancement in renal cortical perfusion (113). In line with these findings, applying tezosentan, a dual ETA/ETB antagonist, in rats with CHF induced by myocardial infarction abolished the enhanced renal vascular resistance (RVR) and improved RBF and urinary salt excretion (114). These encouraging observations were backed up by several studies that have shown beneficial effects of chronic selective ETA blockers (115, 116) or dual ETA/ETB receptor antagonists (117) in experimental CHF, as was evident by relieving sodium retention and mitigating renal hypo filtration. Unfortunately, comprehensive clinical trials failed to show beneficial effects on morbidity and mortality (108). What else, fluid retention and elevated serum transaminase levels were important adverse effects of ET receptor antagonist agents, especially when using non-selective compounds (118). Therefore, proving the involvement of the ET system in the deranged renal hemodynamic and impaired excretory function in CHF and its therapeutic relevance in this clinical setting requires further study.

Vasodilatory and natriuretic systems
Natriuretic peptides

The natriuretic peptides (NPs) system plays a crucial role in maintaining cardio-renal homeostasis by opposing the abovementioned vasoconstrictor, anti-diuretic, anti-natriuretic, and tissue remodeling factors/pathways (119–121). The NP system includes two cardiac hormones, ANP and BNP. Under normal conditions, ANP and BNP are expressed mainly in the heart, with the appendages of the atria being the major site. Previous studies have shown that ANP and BNP encoding genes (*NPPA* and *NPPB*, respectively) play an important role already in the evolvement of the murine fetal heart (122). *NPPA* and *NPPB* lead to the translation of preprohormones (preproANP and preproBNP, respectively). Cleavage of the signaling tail of these peptides produces the inactive prohormones that are designated to undergo further cleavage by corin and furin enzymes to produce the potent peptides ANP and BNP, consisting of 28 and 32 amino acids, respectively (123–126). Both ANP and BNP contain an N-terminal tail and a 17 amino acid ring linked by a disulfide bond. The latter is crucial for the peptides' biological activity. An additional C-terminal extension grants the peptides the ability to signal through the NP receptor. In the atria, the mature and activated BNP, and the proteolytic product N-terminal proBNP (NT-proBNP), together with the unprocessed proANP, are stored intracellularly within mature vesicles, which serve as a warehouse for regulated basal secretion of NPs (119). However, stimulated secretion of ANP and BNP occurs *via* three pathways. Atrial/ventricular wall distention and

intracardiac volume overload enhance NPs secretion through the $G_{o/i}\alpha$-coupled receptor, resulting in higher levels of ANP and BNP in plasma (127). Through the $G_q\alpha$-coupled receptor, several secretagogues, like Ang II, phenylephrine, and ET-1, may induce the same effect (128). In contrast, inflammatory and bacterial lipopolysaccharides may augment BNP, but not ANP secretion, through different pathways leading to p38 activation (129). Interestingly, studies have demonstrated that stimulated secretion of ANP and BNP happens in a constitutive-like manner, meaning *de novo* ANP and BNP are secreted first, and preferentially *via* immature, rather than mature vesicles, as opposed to basal secretion (130).

A third hormone in the NPs system is named C-type NP (CNP). CNP is expressed mainly in the central nervous system, vascular endothelial cells, and kidney, where it functions primarily as a local autocrine/paracrine hormone. Despite its structural similarity with ANP and BNP, CNP lacks a C-terminal extension, and thus does not have natriuretic activity, and its secretion is not regulated by the heart.

The NPs exert their biological activities through natriuretic peptide receptors NPR-A and NPR-B. ANP and BNP recognize and bind NPR-A, and in a considerably less affinity to NPR-B. The latter constitutes the major binding receptor for CNP. NPR is a transmembrane receptor containing an intracellular domain with guanylyl cyclase (GC) activity. After binding to the receptor, ANP/BNP induces a conformational change in NPR-A leading to the activation of GC and a subsequent elevation in intracellular, plasma, and urine cGMP levels (119). By activating the GC in the various target tissues, ANP and BNP induce numerous effects, including natriuresis, diuresis, anti-fibrosis, anti-proliferation, and vasorelaxation, in addition to lowering blood pressure and cardiac preload. A third receptor, NPR-C, lacks the GC-coupled intracellular domain and acts as a clearance receptor through the internalization and degradation of NPs (119).

Natriuretic peptides blunted response in heart failure

In HF, ANP, and BNP secretion is significantly enhanced, and their plasma levels are substantially elevated (131–133). Today, NT-proBNP and BNP plasma levels serve as clinical biomarkers of choice for diagnosing acute decompensated heart failure (ADHF) and are also used as prognostic biomarkers (33, 134–136). An international study suggested incorporating NT-proBNP as a continuous measure along with other clinical variables to provide a more consistent, accurate, and individualized approach to HF patients (137). Nonetheless, one of the paradoxes seen in HF patients is the attenuated NPs effects despite their exceptionally elevated circulating levels in the plasma (138, 139). This phenomenon of NPs resistance/blunted response in HF has been of great interest for researchers in the last two decades, and many mechanisms have been suggested to explain the apparent paradox as outlined below:

Hemodynamic alterations: Hemodynamic changes and the decrease in CO along with a subsequent decline in renal perfusion occurring in HF, which have been widely studied and are well defined (6, 140), might be of paramount significance in the pathophysiology of renal hypo-responsiveness to NPs. NPs have been shown to undergo free filtration in the glomeruli and exert their biological effects in renal tubuli. In addition, HF syndrome is characterized by substantially elevated neurohormonal factors including Ang II, aldosterone, ADH, ET-1, and the SNS, all of which contribute to the attenuated renal and systemic effects of ANP and BNP (see above). Thus, poor renal blood perfusion, and the state of neurohormonal overactivation, may be key players in the attenuated effects of NPs in the kidney.

Post-translational modifications of natriuretic peptides: The abundance of the less-active forms of natriuretic peptides can be a result of post-translational modifications, which have been demonstrated by several studies to have the ability to modulate the activity, stability, and potency of NPs. This important fine-tuning ability can be achieved by the process of O-glycosylation of specific amino acids within the peptide (141–144). Semenov et al. (123, 145) have shown that the processing of proBNP by HEK293 cells expressing human furin and corin enzymes is suppressed by the O-glycosylation at threonine 71 amino acid located closely to the cleavage site. Furthermore, when incubated with purified furin, O-glycosylated proBNP extracted from the plasma of HF patients was significantly less activated when compared to non-glycosylated proBNP.

In another study, O-glycosylation modifications have been identified on all three NPs extracted from porcine heart and human prostate tissues. In addition, two O-glycosylation sites were identified on the mature ANP hormone, both within the highly conserved receptor binding region. Further *in vivo* and *in vitro* assays have demonstrated ANP glycosylation to positively affect circulating half-life by hampering the activity of the NPs degrading enzymes. However, ANP glycosylation negatively affected NPR-A activation. Interestingly, O-glycosylated proANP molecules were found in plasma extracted from human patients with a relatively high concentration of proBNP, estimated to account for 10% of all circulating proANP (146). Vodovar et al. (147) conducted studies on plasma obtained from 683 patients. It was revealed that HF patients had 1.5-fold higher concentrations of O-glycosylated proBNP compared to patients with ADHF or patients with dyspnea of non-cardiac origin. Furthermore, a significant negative correlation was observed between the concentration of glycosylated proBNP and the activation byproduct NT-proBNP, in both ADHF and non-ADHF patients. Moreover, despite having no difference in furin plasma concentrations, the enzyme's activity was extremely high in ADHF patients among all three subgroups. Interestingly, no difference was observed in corin's activity or concentration

between all groups. These observations suggest that post-translational modifications likely occur in any case of chronic, but not acute, overproduction of proBNP.

Altogether, these data suggest an additional explanation for the reduced response to NPs resulted from the post-translational *O*-glycosylation of proBNP, which was shown to be enhanced in chronic HF and reduced in the acute state.

Increase in peripheral degradation and NPR-C clearance: The increase in NPs peripheral degradation and NPR-C clearance occurring in HF may also contribute to this phenomenon. Once released into the circulation, NPs may undergo proteolytic degradation by several enzymes. Neprilysin (NEP), dipeptidyl peptidase 4 (DPPIV), insulin-degrading enzyme (IDE), peptidyl arginine aldehyde protease (PAAP), and meprin-A are all proteolytic enzymes capable of degrading and inactivating the NPs, each having different cleavage site and distinct affinity to the various peptide forms (148–153). One possible explanation for the NPs paradox seen in HF may be the abundance of smaller and inactive NPs as a result of enzymatic degradation in the circulation (154, 155).

In a study published by Dos Santos et al. (156), HF patients exhibited a 130% increase in circulating DPPIV activity compared to healthy subjects, with an inverse correlation between the increase in enzyme activity and left ventricular ejection fraction (LVEF). Similar findings were observed in rats with HF compared to sham-operated animals, with the former demonstrating an increase in both the abundance and the activity of DDPIV, both in the plasma and in heart tissue (156). Furthermore, when treated with a DDPIV inhibitor for 6 weeks, HF-induced rats exhibited a significant attenuation of left ventricle end-diastolic pressure, systolic performance, chamber stiffness, cardiac remodeling, and pulmonary congestion.

In another study conducted by Bayes-Genis et al. (157), it was demonstrated that in patients with HF, circulating levels of NEP positively correlated with hospitalization and cardiovascular death. Interestingly, upregulation of mRNA and immunostaining of NEP in the kidneys of rats subjected to different HF models was evident (158). These findings were of paramount importance as they provided a scientific rational for the development of drugs aimed at targeting NEP for clinical use. Indeed, studies have shown that dual blockade of AT1R and NEP in HF patients was more efficient in reducing the mortality from cardiovascular causes or hospitalization due to worsening HF than was ACE inhibition alone (159, 160). Moreover, combined inhibition of AT1R and NEP led to a greater reduction in NT-proBNP serum levels in patients admitted with ADHF, as compared to ACE inhibitors alone (161). These data indicate that NEP plays a major role in HF syndrome and eliminating its action is beneficial in HF patients.

In addition to catalytic degradation, evidence suggests an increase in NPs clearance *via* NPR-C in patients with HF (158). As expected, blockade of the NPR-C in experimental HF induced a dose-dependent increase in ANP and cGMP plasma levels, as well as natriuresis and diuresis (162). These findings shed light on the adverse role of NPs clearance in HF, which along with NPs peripheral degradation contribute to the NPs paradox seen in HF.

Altogether, these data suggest that NPs degrading enzymes, including DPPIV and NEP, together with increased intracellular clearance, may play a crucial role in the development of NPs blunted response in HF.

Downregulation of NPR-A receptors and changes in downstream signaling: Downregulation of NPR-A receptors and changes in downstream signaling might play an important role in this state of hyporesponsiveness to NPs. The increase in NPs degradation and clearance may partially explain the NPs paradox in HF, especially the blunted response to the administration of synthetic active NPs seen in patients with HF (163). Several studies conducted on HF patients and HF models of experimental animals have suggested a downregulation of NPR-A activity and expression in different tissues, including the kidney (139). It should also be emphasized that elevated expression of phosphodiesterase-5 (PDE5), a cGMP hydrolyzing enzyme, might also contribute to renal hyporesponsiveness to NPs (139). These data shed more light on the complexity of HF syndrome and suggest that multiple mechanisms underlie the renal hypo-responsiveness to NPs in HF.

Aberrant natriuretic peptides activation: In addition to the abovementioned factors and mechanisms involved in the pathogenesis and the development of the NPs paradox in HF, the NPs machinery might constitute a major player in the evolvement of this pathological state. An aberrant machinery system unable to meet the body's requirements in HF, in which it is incapable of producing and/or secreting mature and active hormones, may lead to a pathological state of NPs deficiency and a subsequent neurohormonal imbalance.

Corin is a type-II transmembrane serine protease expressed mainly in the heart (164, 165). By converting proANP and proBNP to their active forms through precise and regulated enzymatic cleavage (124, 125), corin is an important regulator of water and sodium balance, blood pressure, and cardiac remodeling. Therefore, disruption of its expression and/or activity may contribute to the development of several cardiovascular diseases (166–173).

Despite its crucial role, only a few experimental and clinical studies examined the status of cardiac corin under pathological conditions. Moreover, the reported findings were inconsistent. While some studies demonstrated upregulation of corin, others reported down-regulation of this enzyme in HF (168, 174–180). These conflicting results may stem from the application of different models of HF, the duration of HF, the studied chamber of the heart, and more. Yet, the demonstration of decreased cardiac levels of corin in HF may subsequently suggest poor and insufficient activation of NPs and thus partially explain the

aberrant renal response to NPs. In this context, the functional role of cardiac corin in HFrEF was experimentally demonstrated by the genetic restoration of reduced cardiac corin levels in mice with DCM, where it caused improvement of contractile function, suppression of pleural edema, and extended lifespan through cleavage of the pro-ANP and cGMP modulation (168, 181). However, restoration of depressed cardiac corin expression improved systolic function and reduced HF-related systemic and pulmonary edema along with attenuation of HFrEF and survival prolongation through mechanism(s) independent from proANP cleavage (182).

Additionally, corin is also found in the blood system in its circulating forms. Previous studies demonstrated the decreased concentration of soluble circulating corin in patients with HF and acute myocardial infarction, compared to healthy individuals (183–191). Noteworthy, clinical studies demonstrated that decompensated heart failure, assessed by edema and elevated plasma ANP/BNP levels, is associated with reduced corin levels and decreased cleavage of proANP/proBNP peptides (179, 192–195). These observations suggest an inefficient activation of secreted pro-natriuretic peptides which conceivably contributes to HFrEF decompensation (191, 194, 195). In contrast to these findings, Wang et al. (192) reported that acute myocardial infarction (<72 h) induces elevated levels of circulating corin along with a decrease in cardiac corin levels. Interestingly, plasma corin levels were inversely correlated with heart function at the early phase of acute myocardial infarction, thus may reflect the severity of myocardial damage.

Moreover, corin is synthesized as an inactive zymogen and is subsequently activated by proprotein convertase subtilisin/kexin-6 (PCSK6) (196, 197). One might suggest that disturbance in the expression and/or activity of PCSK6 may lead to inactivated corin, and subsequently unprocessed and inactive natriuretic peptides. Recently, we demonstrated decreased cardiac PCSK6 expression and immunoreactive levels in rats with decompensated HF (198). To the best of our knowledge, up to date, there is still no additional data concerning PCSK6 cardiac and circulating abundance or activity in HF, and its contribution to cardiac remodeling, corin activation, and natriuretic peptide processing in this context is unknown.

Inaccurate immunoassays: An additional contributing factor may be the increase in the secretion of the less active forms of BNP seen in HF patients, rather than the mature active hormone BNP_{1-32}. These peptides include NT-$proBNP_{1-76}$, $proBNP_{1-108}$, and additional small peptides resulting from peripheral enzymatic degradation and include BNP_{3-32}, BNP_{5-32}, and BNP_{8-32} (199–202). Today, different commercial immunoassays are available for detecting NT-$proBNP_{1-76}$ and BNP_{1-32} in human plasma. Importantly, these assays can also detect other less-active forms of BNP, whether as a result of degradation or glycosylation, and their

specificity and sensitivity depend on the cross-reactivity of each assay (155).

A study by Hawkridge et al. (203) measured the active BNP_{1-32} levels in the plasma of four HF patients using mass spectrometry. Surprisingly, the group did not detect BNP_{1-32} in these plasma despite the substantially high levels of BNP_{1-32} reported by using commercial immunoassay on the same plasma. An additional study by Seferian et al. (204) revealed that $proBNP_{1-108}$ is the major immunoreactive BNP form in plasma of HF patients, by using specific monoclonal antibodies.

Thus, the high circulating-BNP-levels state seen in HF can be misleading, as these elevated levels may primarily reflect both the inactive and the less potent forms of NPs. In this case, while high circulating BNP levels may constitute a reliable biomarker for HF, patients may be in a state of natriuretic peptide deficiency.

Renal venous congestion

The observation that elevated CVP results in increased outflow pressure in the renal veins in association with renal dysfunction has been first recognized in 1931 (205). In heart failure patients, several studies showed an association between increased CVP and renal dysfunction (32, 206) (**Figure 2**).

The contribution of renal venous congestion to renal dysfunction in HF is complex, involving multiple contributing mechanisms (**Figure 2**) (7). Increased renal venous pressure increases pressures along the renal vascular tree, thus decreasing RBF (207) and arteriovenous pressure gradient in the glomerulus and thereby decreasing GFR (7).

An increase in renal venous pressure can elevate intrarenal interstitial pressure, which in turn affects the entire capillary bed and the tubules (208–211). The kidney is an encapsulated organ and therefore responds to raised renal venous pressures with a disproportionate elevation in intracapsular pressure, which also leads to increased intrarenal interstitial pressure (212). This leads to compression of the tubules (with relative sparing of the renal cortex), increased tubular fluid pressure, with reduced GFR due to an increase in hydrostatic pressure in Bowman's capsule (210). Increased interstitial pressure may promote tubular inflammation and fibrosis, affect tubuloglomerular feedback and activate neurohormonal systems (213) (**Figure 2**).

However, the pattern of renal venous pressure increase in patients with heart failure is substantially different from those used in experimental models, where renal venous pressure was abruptly raised to extremely high values that are usually not seen even in patients with severe heart failure (e.g., 25–50 mm Hg) (209, 210, 213, 214). For example, in the isolated perfused rat kidney model, GFR was not significantly altered until the imposed venous pressure reached 25 mm Hg (210). In a dog model of renal vein hypertension, renal dysfunction occurred only when cardiac output was concomitantly reduced

(24). Notwithstanding, it is possible that the kidneys are more sensitive to elevated CVP in the setting of chronic heart failure, such that GFR may fall with lower CVP than required in healthy animals (215).

In experimental models, renal dysfunction secondary to venous congestion is potentially reversible, at least partially. Lowering renal vein pressure immediately improved its associated renal hemodynamic derangements, leading to improved urine output and GFR. Clinically, the potential for reversibility is demonstrated in patients who show improved renal function after decongestive therapy with diuretics or patients with improvement in right ventricular function secondary to a reduction in pulmonary pressures (216–218).

Mullens et al. were the first to report that elevated CVP was associated with WRF in severe HF with reduced cardiac index who required inotropes or vasodilators (32). In this study, the association between baseline venous congestion and worsening renal function was stronger than the association with CO.

However, the findings of this initial report were not consistent. In subsequent studies, the magnitude of reduction in CVP did not result in improvement in renal function or lower incidence of WRF (219–221).

The effect of the reduction in venous pressure may be difficult to demonstrate clinically given that pressure has little correlation with volume in the venous system (222). Veins have a high compliance and are easily able to accommodate changes in blood volume. The compliant nature of the venous vessels (which contain > 70% of total blood volume) establishes a relative pressure-volume disconnection, allowing large changes in blood volume to be associated with small changes in pressure. Thus, even an effective treatment of volume overload may not be sufficient to produce a meaningful reduction in CVP and, in turn, in renal function.

More recent attempts to prove this concept clinically in patients with HF involve a device-based direct reduction (rather than with diuretics and vasodilators) of renal vein pressure. Revamp Medical developed the percutaneous Doraya catheter, which is positioned infra-renally (223). The distal frame opening can be adjusted to produce a partial obstruction of the venous flow at this level, thus resulting in a reduction of renal venous pressure. The first-in-human study of the Doraya catheter in acute heart failure patients (NCT03234647) demonstrated a substantial pressure reduction at the level of the renal veins (12.4 ± 4.7 mm Hg compared to baseline). This was associated with an increase in urine output from 77.1 ± 25 mL/h at baseline, to 200.8 ± 93 mL/h during device deployment on a stable diuretic dose (223).

Magenta Medical developed a transcatheter renal venous decongestion system designed to reduce the pressure in both renal veins using an axial-flow pump-head positioned in the inferior vena cava (IVC). Two sealing elements are positioned above and below the kidneys to compartmentalize the renal segment of the IVC and allow

selective reduction of renal venous pressures. A clinical trial (NCT03621436) is underway.

Intra-abdominal pressure

The renal consequences of intra-abdominal hypertension (IAH) secondary to fluid overload and visceral edema, and its association with acute kidney injury (AKI), have been first recognized in critically ill patients such as those with abdominal surgery, trauma, and major burns (7, 224, 225). More recently, this entity has been implicated as an important contributor to renal dysfunction in HF based on animal (215, 226) and human (227) studies.

The normal intra-abdominal pressure (IAP) ranges from 4 to 7 mmHg (228). IAH is defined as a sustained or repeated abnormal increase of IAP to ≥12 mmHg (224, 228). However, given the susceptibility to renal dysfunction in heart failure, there are data suggesting that even smaller increases in IAP, in the range of 8–12 mm Hg, can induce a reduction in GFR and sodium excretion (215, 229).

The deleterious effects of IAP on the kidney are closely linked and overlap with those of the aforementioned pathophysiology of venous congestion (**Figure 2**) and congestive nephropathy (227). There is a direct compression of abdominal contents that result in a prominent reduction in RPF (compression of renal arteries) and elevation in renal parenchymal and renal vein pressures (228). The abdominal perfusion pressure (APP) is defined as the difference between the mean arterial pressure and the IAP. As IAP increases, the perfusion of organs or vessels in or near the abdomen falls even with normal mean arterial pressure (224).

In normal physiologic states, hydrostatic pressure in Bowman's space (and therefore in the proximal tubules) is negligible, promoting glomerular filtration; in the presence of IAH, Bowman's space and proximal tubular pressure will be increased close to IAP, resulting in reduced GFR (214, 224, 230). The decreased glomerular hydrostatic pressure (due to hypoperfusion) also contributes to the reduction in the glomerular filtration gradient (225). Elevated IAP also up-regulates the RAAS (231). Because IAH increases renal venous pressure, which in turn produces renal interstitial congestion, the result is a vicious cycle that further increases IAP and renal venous pressure (224).

A reduction in IAP with paracentesis leading to improvement in kidney function has been reported in hepatorenal syndrome (224). Because the majority of patients with IAH are hypervolemic, systemic volume removal also leads to a prompt decrease in IAP and concomitantly improves renal venous hypertension (232).

Few data are available on IAH in HF. A study of 40 patients has shown that 24 (60%) had elevated IAP and 4 (10%) demonstrated IAH despite the absence of overt ascites

(229). A higher prevalence of impaired renal function was observed in patients with IAP, and improvement in kidney function was associated with a reduction of IAP. In a small prospective analysis of patients with acute heart failure, diuretic resistance, and mild IAH, a reduction in IAP with ultrafiltration or paracentesis (if ascites were present) resulted in an increase in urine output and a reduction in serum creatinine (227).

Currently, few data are available regarding the indications to measure IAP in patients with HF and fluid overload. If IAH is documented, prompt volume removal must be considered to decrease IAP.

Edema therapy in heart failure

Congestion is also a hallmark of HFpEF and is associated with adverse outcomes (233, 234). Patients with HFpEF and HFrEF present acutely with comparable clinical and echocardiographic evidence of venous congestion and renal dysfunction (235).

In addition to salt and fluid retention, congestion can also be triggered by fluid redistribution (236, 237). Blood redistribution across different compartments may lead to rapid changes in systemic and pulmonary venous pressures despite constant total blood volume (238, 239). For example, sympathetic activation can increase preload by a functional shift of blood from the splanchnic venous reservoir to the central vascular compartment (222). A rapid increase in systemic pressure and systemic vascular resistance, leading to afterload mismatch may also trigger symptoms in patients with excessive afterload sensitivity and impaired preload reserve (240).

Current recommendations for the treatment of hospitalized patients with fluid overload (241–243) adopt an algorithm originally used in the CARRESS-HF trial (244) (**Figure 3**). The algorithm entails a stepped pharmacologic care that ensures appropriate diuretic doses, with frequent monitoring of urine output and clinical response (**Figure 3**) but has not been rigorously validated in clinical trials.

Diuretics

The efficacy of the diuretic effect is assessed by measuring urine output and spot sodium urine concentration, where effective diuresis is defined as urine volume of >100 to 150 mL/h or urine spot Na+ >50–70 mEq/L with a urine output goal of 3–5 L/day (241). Of note, fluid intake during decongestive therapy can be substantial, such that net fluid loss remains small despite apparently satisfactory urine output. In one study, fluid intake exceeded 50% of urine output in two-thirds of the patients (245). In addition, the patient's weight is not considered in these protocols. A urine output of 2 L/day can be interpreted differently in a patient weighing 70 or 110 Kg.

When this goal is not met, doubling the diuretic dose is recommended. Because the dose-response relationship of a loop diuretic is log-linear, the natriuretic response to each double the dose of a loop diuretic may be modest (246, 247). The addition of oral metolazone or chlorothiazide may provide a greater natriuretic response and urine output (248, 249), with an increased risk for hypokalemia, hyponatremia, worsening renal function, and hypotension (249). The addition of acetazolamide to loop diuretic therapy in patients with acute decompensated heart failure resulted in a higher incidence of successful decongestion (250).

Recently, sodium-glucose co-transporter 2 (SGLT2) inhibitors have been shown to induce significant natriuresis, particularly when added to loop diuretics (251–253).

The usual goal is complete decongestion, with the absence of signs and symptoms of elevated resting filling pressures, because rehospitalization rates and mortality are considerably lower in patients who are free of clinical congestion at the time of hospital discharge (241, 242). However, complete decongestion can be hampered by several factors including low cardiac output, dominant right heart failure and severe pulmonary hypertension, severe renal dysfunction, low plasma oncotic pressure, and symptomatic hypotension (242). For these patients, the goal of edema resolution may need to be relaxed. For example, patients with right ventricular dysfunction, pulmonary hypertension, and tricuspid regurgitation often cannot be decongested to a normal jugular venous pressure. Currently, there is a great interest in novel clinical approaches to treat decongestion. Ongoing clinical trials of drugs or devices for the treatment of congestion are depicted in **Table 1**.

Renin-angiotensin-aldosterone system inhibitors

Renin-angiotensin-aldosterone system inhibitors significantly improved morbidity and mortality in chronic HF patients with HFrEF (260). The beneficial effects of RAAS blockers in HFrEF occur at the cardiac and vasculature levels, yet they induce a reduction in GFR and WRF due to efferent vasodilation, thus increasing the risk of poor clinical outcomes although the mortality benefit is maintained (53, 89, 261). Evidence for the involvement of the RAAS in the development of elevated sodium balance can be derived from studies showing that the renal and hemodynamic response to ANP is impaired in experimental CHF of various etiologies, and that administration of either ARB or ACE inhibitor restores this blunted response to ANP (13). In the last two decades, the adverse role of aldosterone in the pathogenesis of CHF was established (262). Besides promoting sodium retention, aldosterone contributes to vascular and cardiac remodeling by inducing perivascular and interstitial fibrosis (262, 263). Therefore, the addition of small doses of spironolactone or finerenone to standard therapy

FIGURE 3
Algorithm for decongestive therapy.
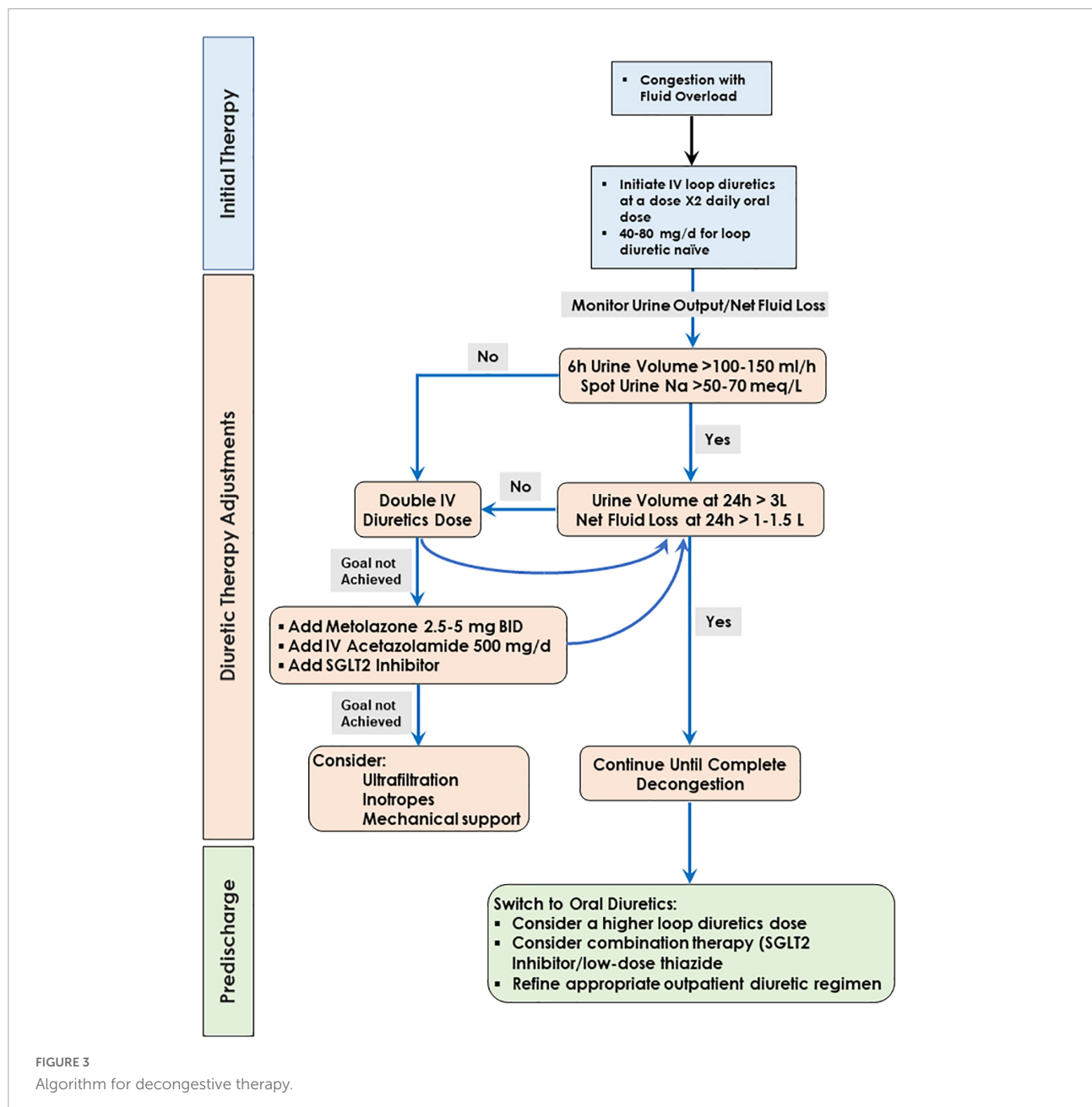
substantially reduces the mortality rate and morbidity in CHF patients (262, 264, 265). At the renal level, RAAS blockers induce diuretic and natriuretic responses, especially at the initial stages of their administration (266).

Beta-blockers

When given with ACEi or diuretics, β-blockers have been shown to reduce mortality and morbidity in patients with HFrEF (267). Beta-blockers should be initiated in clinically stable, euvolemic patients at a low dose and gradually increased

to the maximal tolerated dose. Since activation of the β1 receptor stimulates renin secretion, one may assume that the beneficial effects of β-blockers at both the cardiac and renal levels are partially attributed to attenuation of renin secretion.

Sodium-glucose co-transporter 2 inhibitor

Several clinical trials have demonstrated that SGLT2 inhibitors cause a significant reduction in HF hospitalization (268–270). These beneficial effects on HFrEF patients persist

TABLE 1   Ongoing clinical trials of drugs or devices for the treatment of congestion in HF.

Study	ClinicalTrials.gov identifier	Agent/Device	Clinical setting	Hypothesis
ADVOR trial (254)	NCT03505788	Acetazolamide	AHF	Acetazolamide improves decongestion when combined with loop diuretic therapy in AHF
AVANTI trial (255)	NCT03901726	Pecavaptan, a dual V1a/V2 AVP receptors antagonist	AHF	Pecavaptan improves decongestion when combined with loop diuretic therapy in AHF
TRANSFORM-HF trial (256)	NCT03296813	Torsemide	Stable HF	Torsemide comparative-effectiveness trial of torsemide versus furosemide
REVERSE-HF	NCT05318105	Ultrafiltration – Aquadex system	AHF	Ultrafiltration versus IV diuretics in worsening heart failure
DICTATE-AHF trial (257)	NCT04298229	Dapagliflozin	AHF	Efficacy and safety of initiating dapagliflozin within the first 24 h of hospitalization in patients with AHF compared to usual care
Reprieve cardiovascular system (258)	NCT05015764	Reprieve system	AHF	Reprieve system, which continuously monitors urine output and delivers a matched volume of hydration fluid sufficient to maintain the set fluid balance rate, compared with standard diuretic-based regimen improves decongestion in AHF
Aortix CRS pilot study	NCT04145635	Aortix pump	Cardiorenal syndrome	An elevation of the safety and performance of the Aortix system for intra-aortic mechanical circulatory support in patients with cardiorenal syndrome
SAHARA study	NCT04882358	Alfapump DSR system	Volume overloaded HF	Feasibility and safety study of the alfapump DSR system in the treatment of volume overloaded heart failure
DAPA ACT HF-TIMI 68	NCT04363697	Dapagliflozin	AHF	Effect of in-hospital initiation of dapagliflozin versus placebo on the clinical outcome of cardiovascular death or worsening heart failure
RELIEVE-HF trial (259)	NCT03499236	V-Wave Interatrial Shunt	Stable HF	Safety and effectiveness of the V-Wave Interatrial Shunt System for improving meaningful clinical outcomes in patients with NYHA functional class II, III, or ambulatory class IV HF

even in non-diabetic patients as was reported by DAPA-HF and EMPEROR-Reduced trials (271–273). Specifically, dapagliflozin significantly reduced the primary endpoint of worsening HF or cardiovascular death in the non-diabetic and diabetic groups, respectively, showing its similar efficacy regardless of the presence or absence of diabetes (273). Similar results were obtained by The EMPEROR-Reduced trial, where empagliflozin reduced the combined primary endpoint of cardiovascular death or HF hospitalization by 25% (272). In both DAPA-HF and EMPEROR-Reduced trials, attenuation of eGFR decline was observed following its greater initial drop due to the reduced glomerular hyperfiltration. The mechanisms underlying these beneficial effects include improvement in insulin secretion and sensitivity, osmotic diuretic and natriuretic effects, and resulted reduction of preload and afterload, augmentation of loop diuretics natriuretic action, improvement in myocardial energetics, increase oxygen delivery to the failing myocardium secondary to hemoconcentration, anti-oxidative stress and anti-inflammation (268, 274). At the renal level, SGLT2 inhibitors exert cardiorenal protection beyond these

effects, where their natriuretic action due to inhibition of SGLT2 at the proximal tubule and increased sodium to macula densa activates tubuloglomerular feedback (TGF) as evident by afferent arteriole vasoconstriction, thus preserving renal function as well as improve renal outcomes observed in patients with HF (268, 274).

Sacubitril/valsartan

Since either ARBs or neprilysin inhibitors have shown to improve cardiac and renal function in both experimental and clinical CHF (1, 268, 275), a combined drug, sacubitril/valsartan (ARNI) was introduced in the last decade and became a key drug for the treatment of HFrEF (276, 277). Recent data demonstrated that sacubitril/valsartan, a combined angiotensin receptor blocker and neprilysin inhibitor, significantly reduced cardiovascular mortality and hospitalization due to worsening HF among HFrEF patients, as compared to an ACEi (160). Besides counteracting the negative cardiorenal effects of the

upregulated RAAS *via* AT1R blockade, inhibition of neprilysin by ARNI increases NPs by preventing their degradation, thus inducing natriuresis, reduction of blood pressure, inhibition of cardiac myocyte hypertrophy, apoptosis, and fibrosis (277).

Summary and conclusion

HFrEF is associated with renal dysfunction, reflecting the interconnection between the heart and the kidney. Multiple mechanisms underlie this interdependence including hemodynamic alterations manifested by insufficient peripheral and renal perfusion, along with activation of neurohormonal systems. Exaggerated activation of these factors results in deleterious effects on both the kidneys and the heart, including sodium and water retention, vasoconstriction, increased central and renal venous hypertension/congestion, as well as increased IAP. The latter was shown to induce renal hypoperfusion and hypofiltration. Besides the activation of vasoconstrictor/anti-natriuretic neurohormonal systems, HF is elevated by levels of NPs, yet their beneficial natriuretic and anti-fibrotic effects are attenuated due to the supremacy of the deleterious neurohormonal systems as evident by persistent sodium and water retention and cardiomyopathy. As our understanding of the pathogenesis of cardiac remodeling and sodium retention characterizing CHF is gradually improving, the introduction of mechanistic-based treatments equivalently increases (243). These include neurohumoral blockers such as β-receptor blockers, ACE inhibitors, ARBs, aldosterone receptor antagonists, besides diuretics, the cornerstone therapy, and most recently SGLT2 inhibitors. All these therapies aimed at reducing cardiac remodeling and restoring normal sodium balance along the euvolemic state (88, 267, 278). Although the application of diuretic therapy is widely adopted in acute decompensated CHF and chronic HF, the need for loop diuretic utilization should be tapered continuously to prevent the rebound of sodium retaining/vasoconstrictor systems. Intriguingly, new drugs in the treatment of chronic HF, which also decrease sodium avidity, have demonstrated improved HF hospitalizations and survival (4). Therefore, the introduction of SGLT2 inhibitors and widening their clinical use beyond diabetes may represent a game changer in the treatment of HFrEF and renal dysfunction.

Author contributions

ZA, EK, TK, and DA drafted the manuscript. ZA, EK, and DA prepared the figures. All authors edited the manuscript and provided constructive comments.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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