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Review

Venous Congestion and Systemic Hypoperfusion in Cardiorenal Syndrome: Two Sides of the Same Coin

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Abstract

A wide range of comorbidities play a pivotal role in worsening outcomes and increasing mortality risk in patients with heart failure (HF). Among them, renal dysfunction has been recognized as a highly prevalent prognostic variable, with a strong impact on prognosis, length of hospital stay and need for intensive care. In this context, recent evidence has pointed out the relevance of both systemic hypoperfusion and venous congestion on the imbalance of renal function as well as on the conditioning the pathophysiological crosstalk between heart and kidneys through a wide range of haemodynamic and biochemical pathways. This narrative review aims to investigate the intricate interplay between impaired systemic perfusion and venous congestion in cardiorenal syndrome, as well as their haemodynamic and biochemical implications for renal damage in HF.

Keywords: heart failure; venous congestion; systemic hypoperfusion; cardiorenal syndrome

1. Introduction

Despite the new insights concerning the therapeutic strategies for heart failure (HF), its prognostic outcomes remain unfavourable, with a high mortality and considerable impact on the quality of life [1]. A wide range of clinical comorbidities play an important role associated with poorer outcomes and increased risk of mortality in HF patients. Among them, renal dysfunction has been recognized as highly prevalent prognostic variable, affecting nearly 60% of patients hospitalized for acute decompensated HF, and whose impact on prognosis, length of hospital stay and need for intensive care, increases in proportion to the degree of baseline renal failure [2]. In this context, the bidirectional pathophysiological cross-talk between kidneys and heart leads to the definition of cardiorenal syndrome (CRS), whose classification has been proposed at the Consensus Conference of the Acute Dialysis Quality Initiative [3] (Table 1). Recent evidence has suggested that both impaired cardiac output and increased central venous pressure may actively contribute to renal deterioration in HF, although their respective contribution are currently a matter of extensive debate [4,5]. This review aims to investigate the intricate relationship between impaired systemic perfusion and venous congestion in CRS, as well as their haemodynamic and biochemical implications on renal damage in HF.

2. Data from the Literature

In the last decades, renal deterioration in HF has been attributed solely to renal hypoperfusion as a primary pathophysiologic trigger, caused by cardiac failure in generating adequate forward flow, as a result of reduced cardiac output with consequent progressive deterioration of renal function. In this pathophysiological context, several neurohormonal pathways, such as the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, play a key role in driving systemic vasoconstriction, in order to maintain an adequate glomerular filtration rate (GFR) and preserve renal function [6,7]. This pathophysiological paradigm has been recently challenged by several investigations that have shown no correlation or even paradoxical correlation between pump failure and renal dysfunction. Data from ADHERE (Acute Decompensated Heart Failure National Registry) highlighted an overlapping incidence of renal derangement in patients with reduced or preserved ejection fraction, thus resizing the pathogenic role of systemic hypoperfusion in this clinical setting [8]. Furthermore, a post-hoc analysis of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) randomized trial by Nohria *et al.* [9] showed a lack of correlation between baseline renal function and cardiac index in patients hospitalized for advanced decompensated HF, thus suggesting that reduced systemic perfusion might not be the sole cause of renal impairment in HF. These data were reinforced by the analysis of Hanberg and colleagues [10], in which no association between renal failure and low systemic perfusion was reported across multiple subgroups of subjects, with different metrics of renal function and spectrum of cardiac index. On the other hand, venous congestion has been largely detected in HF patients. However, its hypothetical role in worsening renal function has always been considered a secondary haemodynamic determinant consequent to the decreased stroke volume, despite experimental animal data collected since 1930s revealed a direct renal impairment

Table 1. Classification of CRS based on the conference of the acute dialysis quality initiative.

Type	Denomination	Description
CRS type 1	Acute cardiorenal	HF leading to AKI
CRS type 2	Chronic cardiorenal	Chronic HF leading to CKD
CRS type 3	Acute renocardiac	AKI leading to acute HF
CRS type 4	Chronic renocardiac	CKD leading to chronic HF
CRS type 5	Secondary	Systemic disease leading to heart and kidney failure

AKI, acute kidney injury; CKD, chronic kidney disease; CRS, cardiorenal syndrome; HF, heart failure.

induced by the backward transmission of increased central venous pressure [11,12]. Even earlier, in 1861, Ludwing had reported slow urinary flow associated with progressive increase in right atrial pressure, that he attributed to kidney congestion [13]. However, in recent years human data focusing on the interrelation between kidney congestion and renal dysfunction have revalued this topic. Examining a cohort of subjects with advanced decompensated HF, Mullens and co-workers showed that venous congestion was the strongest driver for renal impairment, while little contribution was given by systemic hypoperfusion [14]. Similar evidence was found by Guglin *et al*. [15] in a different subset population, who underwent haemodynamic evaluation as part of their routine HF diagnostic work-up. Overall, these data show how both the haemodynamic variables of cardiac preload and those of renal perfusion seem to play a role at various levels of renal impairment in patients with HF.

3. Cardiorenal Interactions, Comorbidities and Haemodynamic Variables in Heart Failure

The intricate interplay between venous congestion, reduced systemic perfusion and renal impairment is a challenging pathogenic framework, in which multiple haemodynamic variables play a critical role [5]. Among the main determinants of renal circulatory function, renal blood flow (RBF) is defined as the volume of blood delivered to the kidneys per unit of time. It normally reaches roughly 20% of the total cardiac output, amounting to approximately 1 L/min in a 70 kg adult male, and it is closely related to the renal plasma flow, defined as the volume of blood plasma per unit of time. RBF is proportional to the difference between renal arteries and veins al and venous pressure, while it is inversely related to renal vascular resistances. Another crucial parameter of renal function is related to the estimated GFR, which describes the fluid rate of blood flow filtered through the kidneys [16]. GFR is linked to RBF, as with Starling forces between the glomerular capillaries and the Bowman space. Finally, filtration fraction is defined as the fraction of renal plasma flow filtered across the glomerular capillaries which reaches the renal tubules. Its normal value is nearly 20%. However, it has to be a dynamic variable on the basis of changes in renal perfusion, in order to maintain the physiologic functions of the kidney [17,18]. Although the paradigm that a reduction in systemic perfusion will trigger a decrease in the estimated GFR apparently seems to be extremely rational, it appears oversimplified. Renal perfusion is normally preserved under strict local control, within a certain range of renal arterial perfusion pressure, between 80 and 180 mmHg, by two intrinsic and interdependent mechanisms of autoregulation: a fast component related to myogenic vasoconstriction, and a slow component derived from the tubuloglomerular feedback (Fig. 1) [19]. In case of low renal perfusion, a fall in renal arterial pressure will reduce fluid and Na^+ delivery to the distal nephron, thus increasing oncotic pressure while reducing hydrostatic pressure in the peritubular capillaries. Such changes will facilitate Na^+ reabsorption in the proximal tubule and will reduce its availability to the macula densa; the latter in its turn will decrease adenosine triphosphate synthesis and calcium release from the smooth muscle cells of the afferent arteriole, thus leading to arteriolar vasodilatation and renin release, with raised efferent arteriolar tone and increased filtration fraction. The opposite occurs in case of increase in renal arterial pressure, with higher Na^+ delivery to the distal tubule, which in turn will trigger adenosine secretion and will reduce renin release, leading to afferent arteriolar vasoconstriction and lowering RBF. Moreover, adenosine will raise Na^+ reabsorption by proximal and distal tubules, with subsequent venous congestion and decreased renal perfusion [20,21]. As previously reported by Ljungman and colleagues, these autoregulatory pathways fall in case of severe impairment of cardiac index (below 1.5 L/min/m^2) in which a non-compensatory filtration fraction occurs, and GFR becomes dependent on afferent arteriolar flow, despite the activation of haemodynamic and neurohormonal mechanisms to increase the efferent arteriolar tone [22]. Finally, several comorbidities play an essential role in worsening renal function in HF patients. The estimated prevalence of atrial fibrillation in renal disease is significantly higher than in the healthy general population [23]. Several mechanisms are responsible for a bidirectional crosstalk between renal impairment and HF. Activation of the RAAS induces renal damage through different inflammatory mediators, including reactive oxygen species (ROS) and transforming growth factor β_1 (TGF-β_1) production, extracellular matrix proteins synthesis and macrophage infiltration. In the same way, oxidative stress

and neurohormonal activation through RAAS and TGF-β_1 synthesis contribute to left atrial fibrosis and remodelling [24,25]. Likewise, left ventricular dilatation leads to higher left-sided filling pressures, which propagate to the atrial wall and predisposes to perpetuating atrial fibrillation and worsening HF [26]. Chronic obstructive pulmonary disease (COPD) is another relevant comorbidity, which severely impacts on prognostic outcomes among HF patients. The pathogenic relationship between COPD and cardiorenal derangement is still debated [27]. In this clinical setting, hypercapnia has been recognized as a pathogenic driver in this clinical setting, as it induces renal vasoconstriction either directly or indirectly by increasing catecholamine plasmatic levels, which in turn predispose to lower RBF, increased tubular Na^+/H^+ exchange, and water retention [28]. On the contrary, hypoxia alone has not been demonstrated to significantly affect renal hemodynamics, although oxygen supply has been shown to induce a vasodilator response and increased renal arterial blood flow. Further investigation is needed to better explain the role of hypoxia in cardiorenal interactions [29,30].

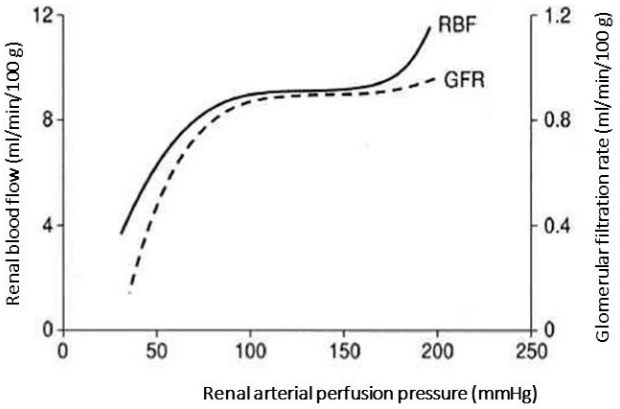

Fig. 1. Schematic view of autoregulation of renal perfusion, which is preserved between 80 and 180 mmHg of renal arterial perfusion pressure. GFR, glomerular filtration rate; RBF, renal blood flow.

4. Differences between Left and Right Heart Failure in Cardiorenal Interactions

Different pathogenic mechanisms play a role in developing CRS, with regard to prevailing left or right ventricular derangement. A decreased RBF and an increased backward renal venous pressure are the mainstream mechanisms leading to kidney deterioration in left ventricular HF [31,32]. Lower renal arterial perfusion pressures are detected both in HF with reduced ejection fraction (due to decreased stroke volume and to systemic hypoperfusion) and in HF with preserved ejection fraction (mainly related to increased afterload). This, in turn, triggers renal and systemic vasoconstriction through neurohormonal activation, with consequent Na^+ and water retention, higher plasma volume and venous congestion due to increased central venous pressure [33]. On the other hand, the mechanisms of kidney deterioration in isolated right ventricular failure are currently debated. Compromised cardiac output consequent to ventricular dyssynchrony and left ventricular septal bowing due to right ventricular pressure overload represent the main mechanisms of renal damage involved in pulmonary arterial hypertension and chronic thromboembolic disease [34,35]. Furthermore, also hypercapnia and hypoxia are involved in decreasing systemic vascular resistances and renal perfusion, particularly in right ventricular failure related to COPD or to obstructive sleep apnoea syndrome [28,33]. Finally, patients with isolated right ventricular dysfunction are more prone to the renal consequences of central venous congestion than those with left ventricular impairment, because in the former renal impairment is worsened by increased right ventricular afterload rather than solely by Na^+ and water retention. Indeed, the effects of water retention on increased renal interstitial pressure and renal hypoxia are related to the retrograde transmission of right atrial pressure to the kidneys [36].

5. Biochemical Mediators of Cardiorenal Disruption in Heart Failure

Several and multifactorial mechanisms are involved in the pathogenesis of CRS, including haemodynamic imbalance as well as neurohormonal activation and inflammatory response (Fig. 2, Ref. [37]).

5.1 Neurohormonal Pathways Involved in Renal Impairment in Heart Failure

For values of renal arterial perfusion pressure below 80 mmHg, renal autoregulatory mechanisms fail. In this pathophysiological context, the neurohormonal axis (including both sympathetic nervous system and RAAS) is upregulated, thus leading to increased levels of angiotensin II and catecholamines, which in turn lead to a disproportionate vasoconstrictive effect on the efferent glomerular arterioles [38]. This response is crucial in order to initially preserve GFR and the filtration fraction, despite the decreased renal plasma flow. However, long-term increased angiotensin II and catecholamines become maladaptive, leading to preglomerular vasoconstriction and reduction of GFR. Moreover, increased angiotensin II concentrations promote renal fibrosis, induce a blunted responsiveness to natriuretic peptides and affect GFR, either directly or by increasing the sympathetic nervous system activity [39,40]. The consequent activation of proximal tubular sodium and water reabsorption leads to raised central venous pressure and backward transmission to the kidneys. The latter is responsible for increased interstitial renal pressure and tubular compression, which result in lower trans-glomerular pressure gradient and decreased GFR [41].

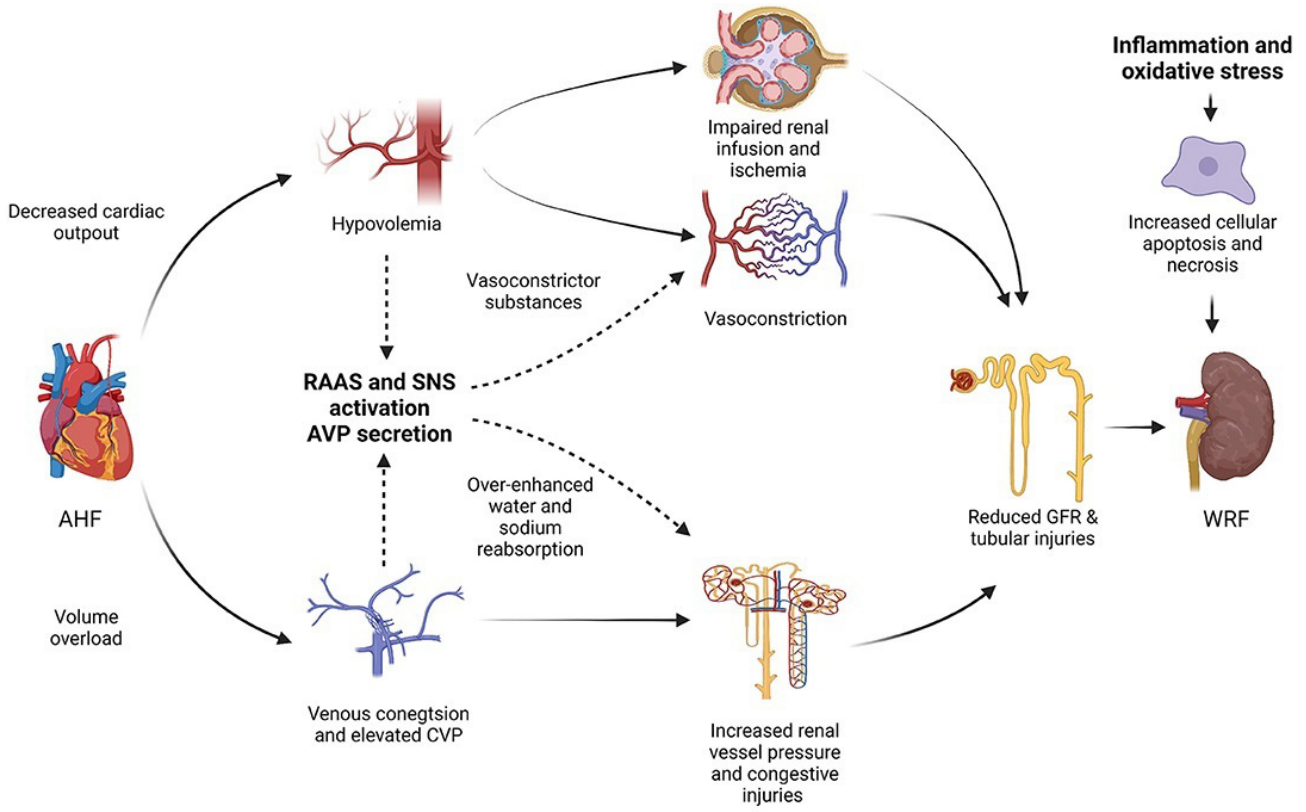

Fig. 2. Pathogenic mechanisms of worsening renal function in cardiorenal syndrome. Adapted from Fu K. *et al*. [37]. AHF, acute heart failure; AVP, arginine-vasopressin; CVP, central venous pressure; GFR, glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; WRF, worsening renal function.

5.2 Dysregulation of Nitric Oxide Pathway and Reactive Oxygen Species

Both venous congestion and systemic hypoperfusion perpetuate kidney injury through the deregulation of the nitric oxide (NO) pathway. NO is an endothelium-derived vasodilator mediator which plays a key role in autoregulation mechanisms, through the modulation of vascular tone, the antagonization of smooth muscle cell hypertrophy and its involvement in tubuloglomerular feedback through afferent arteriolar dilatation [42]. Acute decompensated HF upregulates the renin-angiotensin-aldosterone axis and increases angiotensin II levels, which downregulate the NO pathway and lead to the vasoconstriction of efferent arterioles [43,44]. Furthermore, the derangement of the NO pathway is also promoted by the increased oxidative stress occurring through the reduced activity of the superoxide dismutase enzyme and the raised levels of asymmetric dimethyl arginine. They both contribute to decrease NO plasmatic levels and to enhance the generation of ROS [45]. Finally, increased levels of angiotensin II promote the release of endothelin-1 from endothelial cells, which contributes to antagonize the NO pathway and predisposes to vasoconstriction, vascular remodelling and proliferation, as well as to worsening endothelial dysfunction [46,47].

5.3 Impact of the Arginine-Vasopressin System in Cardiorenal Syndrome

The arginine-vasopressin (AVP) system plays an active role in perpetuating a pathophysiological vicious circle leading to CRS in HF patients. AVP is a neuroendocrine peptide secreted by the paraventricular nucleus of the hypothalamus and stored in the posterior pituitary gland before its secretion. It exerts its actions by binding to its specific receptors: V_{1a}, V_{1b} and V_2. V_{1a} receptors are mainly located in peripheral vascular smooth muscle cells and in the myocardium, and their binding causes vasoconstriction and increases myocardial contractility. V_{1b} (also named V_3) receptors are present in the anterior pituitary gland and their activation is responsible for the secretion of the adrenocorticotropic hormone. Finally, V_2 receptors are located in renal collector ducts, and their activation induces water retention through the insertion of aquaporin-2 channels into the membrane surface [48,49]. Osmotic and non-osmotic pathways are mainly involved in AVP secretion, through different triggering mechanisms. The former includes any change in the plasmatic osmolar state: hypoosmolarity inhibits AVP secretion, while the opposite occurs in case of increased plasmatic osmolarity [50]. Besides, non-osmotic triggers, including a drop in blood pressure and decreased cardiac output, play a crucial role in

releasing AVP in HF. This in turn induces detrimental effects on cardiac function, by increasing cardiac afterload and preload through systemic vasoconstriction and water retention, respectively [48,51].

5.4 Contribute of Abdominal Congestion to Renal Impairment in Heart Failure

Congestive HF is often characterized by inadequate natriuresis, which progressively leads to volume overload and systemic congestion. In this context, splanchnic circulation plays a crucial role in preserving an euvolemic circulatory system, with no detrimental systemic haemodynamic effects. Under physiological conditions, splanchnic capacitance veins involve 25% of total blood volume, which may increase as much as 65% of total volume, in order to maintain a stable effective circulatory volume [52]. In congestive HF, the occurrence of backward failure together with arteriolar vasoconstriction due to systemic hypoperfusion lead to a progressive blood shift from the effective circulatory volume to the splanchnic capacitance veins, which become maladaptive [53]. Therefore, a progressive increase in intra-abdominal pressure (whose normal values range below 5–7 mmHg), leads to intra-abdominal venous hypertension (in case of intra-abdominal pressure $>$12 mmHg) and compromised splanchnic lymph flow vasculature. The latter is a common cause of urinary retention and organ damage and it further contributes to increased cardiac filling pressure and worsening HF [54].

5.5 Inflammatory Response in Cardiorenal Syndrome

Impaired systemic perfusion and venous congestion play a pivotal role in inflammatory response in CRS, with a strong impact on worsening renal function. Arterial underfilling, as well as renal congestion can induce vascular dysfunction through endothelial cell activation, which is responsible for a pro-oxidant, pro-inflammatory and vasoconstrictive state. Moreover, raised filling pressures also induce circumferential elongation of the venous wall and promote the release of pro-inflammatory cytokines (including endothelin-1, tumor necrosis factor-α and interleukin-6), as well as of ROS [55]. Together, they trigger a systemic inflammatory response and tubule-interstitial inflammation, through the activation of the nuclear factor κB. This, in turn, leads to progressive kidney dysfunction, fibrosis and increased endothelial permeability, thus promoting fluid extravasation into lung alveoli and peripheral tissues [56]. Additionally, impaired intestinal barrier secondary to venous congestion may promote the absorption of local bowel toxins into the circulatory system, with further worsening of HF and renal dysfunction [57,58].

6. Risk Stratification and Prognostic Outcomes

The haemodynamic contributions of both increased central venous pressure and reduced cardiac output on worsening renal function, may lead to several consequences in clinical practice. As previously reported by Stevenson and colleagues [59], the presence/absence of clinical signs of congestion (such as orthopnoea, paroxysmal nocturnal dyspnoea, jugular turgor, pulmonary or peripheral bilateral oedema, gut congestion and ascites) and/or impaired organ perfusion (such as the presence of cold sweaty extremities, oliguria, dizziness and narrow pulse pressure) also define four different haemodynamic profiles associated with different prognostic outcomes, which help to guide proper therapeutic strategies. Patients with a ‘wet’ haemodynamic profile show increased pulmonary or systemic congestion related to higher central venous pressure, which in turn impacts on renal venous pressure and renal perfusion pressure, leading to increased interstitial pressure and tubular collapse and predisposing to renal damage [60,61]. Such more congested cardiac and renal profiles highly impact on both prognostic outcomes and mortality, as compared to more hypoperfused clinical profiles. Specifically, the ‘wet and warm’ patient profile (in which RBF is generally normal) has a direct impact on survival, with a 6-month mortality of 11%. This clinical profile has shown a minor impact on increased right atrial pressure and worsening renal function. As a consequence, treatments to reduce venous congestion and intra-cavitary filling pressures would have only a limited impact on improving GFR [62]. However, although in this subset of patients renal perfusion is largely preserved, its progressive impairment may lead to a fast worsening of renal function, shifting toward a more unfavourable ‘wet and cold’ profile, which is associated with a 6-month mortality of 40% and has a detrimental effect on survival [14,63]. Therefore, the close relationship between cardiac output and central venous pressure challenges the first intuitive paradigm that fluid overload will invariably lead to a better renal perfusion [64]. In this kind of patients, inotropic treatment together with decongestive and vasodilator therapies have shown to be helpful in preventing acute loss of renal function. Consequently, the improved prognostic outcomes foster a shift toward a more favourable ‘dry and warm’ patient profile [22,65]. On the other hand, euvolemic patient with systemic hypoperfusion, who have a ‘dry and cold’ haemodynamic profile, often require pharmacological inotropic support in order to improve the effective arterial filling volume and the cardiac output, with a consequent increase in renal arterial perfusion pressure and improvement of renal function [66,67]. However, the long-term application of such a medical strategy often results in increased mortality. Therefore, for patients refractory to pharmacological treatment, the use of mechanical circulatory supports is often needed [68]. Taken into account the aforementioned findings, such a method of classification and risk stratification of HF patients should be considered as a prudent attempt to devise a suitable therapeutic strategy [69].

7. Therapeutic Approach

Several preventive measures and treatment options for the management of CRS have been reported in clinical practice. Salt and water restriction in hyponatremic patients have been reported to increase survival and quality of life, as well as more effective strategies in reducing ventricular filling pressures, arterial elastance and atrial remodelling [70,71]. Intravenous loop diuretics are commonly used as the first-line treatment of acute decompensated HF patients, as they reduce fluid overload and soothe clinical signs and symptoms of pulmonary or peripheral congestion [72]. Dosage and frequency of administration of loop diuretics represent another challenging topic for debate in literature. An initial intravenous dose of loop diuretics twice the domiciliary oral dose has been commonly proposed in clinical practice, in order to overcome low intestinal absorption related to splanchnic congestion [73]. To date, data from the literature do not report continuous dosing of loop diuretics as being more effective than optimally prescribed bolus regimen, as revealed by the DOSE (Diuretic Optimization Strategy Evaluation) trial [74]. The prescription of long-acting loop diuretics, such as torasemide, has been proposed to prevent neurohormonal activation related to rebound Na^+ reabsorption [75]. Furthermore, the introduction of different classes of non-loop diuretics (such as thiazide or mineralcorticoid receptor antagonists) as an add-on therapy to intravenous loop diuretics may overcome the escape phenomenon by decreasing Na^+ absorption from the distal tubules. However, this in turn can lead to neurohormonal overactivity, with rebound Na^+ reabsorption, worsening venous congestion and renal function [72,76]. Additionally, in the context of synergic medical treatment, several other novel therapeutic strategies have been proposed. Nesiritide is a recombinant human brain natriuretic peptide that has shown to decrease cardiac filling pressure, RAAS activity and catecholamine release and to increase cardiac output [77]. However, the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial did not demonstrate a significant improvement in prognostic outcomes, compared to placebo [78]. Alternatively spliced brain natriuretic peptides (ASBNP and ASBNP.1) are also involved in increasing the glomerular filtration rate and suppressing plasmatic renin and angiotensin, together without the hypotensive effect of nesiritide [79]. Another topic of interest concerns pharmacological strategies to improve renal function by targeting the AVP system. Since vasopressin contributes to arterial vasoconstriction and water reabsorption through its binding to V_{1a} and V_2 receptors respectively, vaptans are drugs tested in clinical trials, due to their potential benefits in HF [80,81]. In the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) trial, the oral selective V_2 receptor antagonist tolvaptan caused an early and sustained body weight loss without worsening renal function, although it did not impact on morbidity and mortality [82]. Furthermore, among novel therapeutic strategies, relaxin has been proved to induce systemic and renal vasodilatation through its action on NO and endothelin-1. In the Pre-RELAX-AHF trial, relaxin was associated with a relief from dyspnoea and reduction in length of hospital stay, compared to placebo. However, it did not significantly impact on HF death rate [83]. Finally, ultrafiltration has been recognized as a reasonable approach in patients with CRS and refractory venous congestion non responsive to pharmacologic therapy, in order to improve haemodynamics and reduce fluid overload [84]. Compared to diuretic treatment, ultrafiltration is characterized by the following aspects: (i) it allows a predictable and quantifiable fluid removal compared to the urinary output produced by intravenous diuretics; (ii) compared to loop diuretics, ultrafiltration is isotonic and it removes a greater amount of Na^+; (iii) ultrafiltration prevents excessive fluid removal and consequent neurohormonal activation; (iv) along with Na^+ and water removal, ultrafiltration also permits the elimination of vasoactive agents and pro-inflammatory cytokines [85–87]. In this regard, the UNLOAD (Ultrafiltration Versus Intravenous Diuretics For Patients Hospitalized For Acute Decompensated Heart Failure) trial showed a significant increase in weight and fluid reduction, together with lesser HF hospitalization among patients treated with ultrafiltration, compared to the use of intravenous diuretics [88]. However, the CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) trial did not provide sufficient evidence about the superiority of ultrafiltration as a first line therapeutic choice for the preservation of renal function, compared to stepped pharmacological treatment [89]. Alternatively, peritoneal dialysis has been proposed as a therapeutic strategy whose use should be considered in congestive HF patients refractory to diuretic treatment, despite its adverse effects, including increasing intra-abdominal pressure, peritonitis and hyperlipidemia [90,91].

8. Conclusions

In conclusion, a conceptual shift is needed towards considering venous congestion and systemic hypoperfusion as both involved in the pathogenic mechanisms of CRS, like the two sides of the same coin. Their intricate interplay still represents a challenging pathophysiologic framework, knowledge of which appears to be necessary in clinical practice, in order to provide a comprehensive therapeutic approach and the best individualized clinical models.

Author Contributions

RS–manuscript conception, design and writing. CB–critical review and final approval of the manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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