Review

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The congestion "Pandemic" in Acute Heart Failure Patients

Daniela Mocan [1,*,†], Radu I. Lala [1,2,*,†], Maria Puschita [1,*], Luminita Pilat [1], Dan A. Darabantiu [2] and Adina Pop-Moldovan [1,2]

[1] Multidisciplinary Doctoral School, Vasile Goldis Western University of Arad, AR 310025, Romania; luminita.pilat@yahoo.com (L.P.); pop-moldovan.adina@uvvg.ro (A.P.-M.)

[2] Cardiology Department, Arad County Clinical Emergency Hospital, 310037, Arad, Romania; ddarabantiu@yahoo.com

* Correspondence: hoza-mocan.daniela@student.uvvg.ro (D.M.); radu_lala@yahoo.com (R.I.L.); mpuschita.mp@gmail.com (M.P.); Tel.: +40-740147286 (D.M.); +40-727424296 (R.I.L.); +40-722431951 (M.P.)

Abstract: Congestion not only represents a cardinal sign of heart failure but is also now recognized as the primary cause for hospital admissions, rehospitalizations, and mortality among patients with acute heart failure. Congestion can manifest through various heart failure phenotypes in acute settings: volume overload, volume redistribution, or both. Recognizing the congestion phenotype is paramount, as it implies different therapeutic strategies for decongestion. Complete decongestion is hardly achieved among patients with acute heart failure, as more than half still have residual congestion at discharge. Residual congestion is one of the strongest predictors of future cardiovascular events and poor outcomes. Through this review, we try to provide a better understanding of the congestion phenomenon among patients with acute heart failure by highlighting insights into the pathophysiology mechanisms behind congestion and new diagnostic and management tools to achieve and maintain efficient decongestion.

Keywords: heart failure; congestion; volume overload; volume redistribution; biomarkers

1. Introduction

Heart failure (HF) has evolved into a profound global health concern, commanding attention due to its widespread impact and alarming mortality rates. With an estimated 64.3 million individuals affected worldwide and one-year mortality rates ranging between 21% and 36%, HF stands as a great challenge in the realm of public health. As communities grapple with the aftermath of previous health crises, HF underscores the urgent need for a comprehensive understanding and proactive measures to address this escalating global scale issue [1]. According to the new universal definition of heart failure, this condition is considered a clinical syndrome with current/prior symptoms and signs caused by a structural or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and evidence of pulmonary or systemic congestion [2].

Congestion encompasses more than just clinical signs and symptoms, and it appears to be the critical player underlying the complex pathophysiology of heart failure [3].

Various factors determine the clinical course of congestion among patients with acute heart failure, including kidney impairment, volume overload or redistribution, diuretic resistance, electrolyte disorders, low blood pressure, and inflammation. All these factors can lead to incomplete decongestion at discharge, thus influencing prognosis regarding future rehospitalizations and mortality. In this review, by immersing into the pathophysiological mechanisms of congestion, unraveling its phenotypes, and discussing emerging diagnostic tools for targeting decongestive therapy, we aim to acknowledge the importance of 'the congestion phenomenon' and its scale among heart failure patients, which is of pandemic proportions.

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2. Understanding Congestion: Volume Overload or Volume Redistribution

Congestion is manifested clinically through signs and symptoms due to extracellular fluid accumulation due to increased left-sided cardiac filling pressures [3,4]. The increase in cardiac filling pressures is an early indicator of hemodynamic congestion, which precedes the development of congestive symptoms in days or weeks [5]. Congestion leads to heart failure decompensation, which manifests clinically with dyspnea, orthopnea, systemic edema, jugular venous distention, and third heart sound [3,5]. It is important to understand the underlying mechanism that first leads to hemodynamic congestion and then to clinical congestion, so early recognition and proper treatment of this condition is imperative. To do so, one must first identify the transition phase between hemodynamic and clinical congestion.

Congestion results from the combined effects of forward and backward failure of the heart, coupled with the inadequacy of compensatory adaptive mechanisms to counter the detrimental impact of reduced oxygen delivery to peripheral tissues. Reduced cardiac output, as well as systemic venous congestion, results in renal hypoperfusion, thus leading to neurohormonal activation with sodium and water accumulation and consequent volume overload [6]. Sodium (Na) is stored in the extracellular compartment, mainly in the interstitium at 65% and 25% in the intravascular compartment [7].

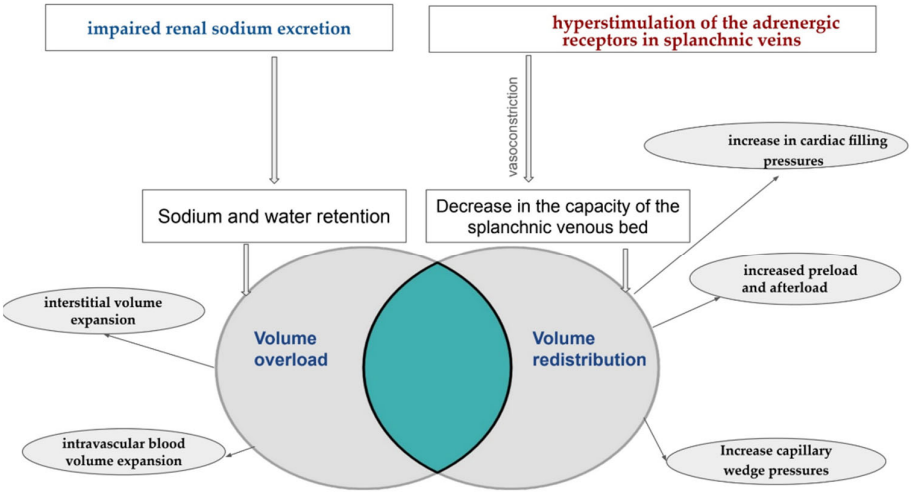

Figure 1. Schematic representation illustrating the interplay between volume overload and volume redistribution in congestion.

Congestion is the cardinal manifestation of both chronic heart failure (CHF) and acute heart failure (AHF). The main mechanisms responsible for venous congestion are volume redistribution and volume overload. The first mechanism describes the rapid distribution of blood volume from systemic circulation to pulmonary venous circulation. It is due to a reduction in the capacitance of the splanchnic venous bed. The first mechanism involves the movement of blood volume from the systemic circulation to the pulmonary venous circulation. This phenomenon is attributed to a decrease in the capacity of the splanchnic venous bed, prompting expedited blood redistribution [8]. Volume redistribution was assessed in three major trials: COMPASS-HF, HOMEOSTASIS–HF, and CHAMPION by invasive monitoring of hemodynamics. All findings consistently indicate that weight gain resulting from volume overload does not typically precede an episode of acute decompensation in most patients; instead, there is an observed increase in cardiac filling pressures [9–11]. Heart failure is a state of neurohormonal activation, inflammation, and endothelial dysfunction that promotes veno-arterial constriction. This leads to a subsequent decrease in venous bed capacitance with consequent blood volume redistribution and increased preload and afterload [12]. Fluid shifts between the interstitial and intravascular compartments occur weeks before the acute event, mostly without weight change. Hyperstimulation of the adrenergic receptors in

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splanchnic veins characterizes the mechanism, increasing cardiac filling and capillary wedge pressures [12]. This rather silent mechanism leads to intravascular volume expansion, thus preparing the ground for what would be the perfect storm. This is termed asymptomatic hemodynamic congestion. Increased cardiac filling pressures lead to myocardial insult, thus triggering the acute event by rapid translocation of up to 1 L of fluid into the interstitial and then the alveolar space with consequent development of worsening dyspnea and clinical congestion [13].

The second mechanism responsible for congestion is volume overload, a rather insidious process with an absolute increase in water and sodium body content [14]. Volume overload is more common in those with cardio-renal dysfunction and chronic heart failure [14]. Venous distension augments endothelial dysfunction and sympathetic activation, further promoting the fall in splanchnic venous capacitance and consequent fluid redistribution [15]. In other words, there is an overlap between these two mechanisms. Fluid retention is caused by impaired renal sodium excretion [14]. Understanding the heart-kidney cross-talk as Na homeostasis, neurohormonal activation, and inflammation impair nephron tubular flow, contributing to Na and water retention [16]. This will lead to increased central venous and intra-abdominal pressure, further worsening renal function [17]. Most Na reabsorption takes place in the proximal renal tubule (65%), mediated by Na transporters and sodium-potassium pump (Na/K ATP-ase) [18]. As Na is reabsorbed, water passively follows the osmotic gradient. This process is kept stable through glomerular-tubular feedback but becomes unstable in heart failure due to deleterious mechanisms. Na reabsorption is promoted in HF in the proximal tubule by increased peritubular oncotic pressure, renal venous pressures, and renal lymph flow [17]. In addition to this, every drop in glomerular filtration rate (GFR) due to worsening renal function decreases the amount of urinary Na excretion. In heart failure, less water and solutes reach the loop of Henle due to increased reabsorption from the proximal tubule [17]. This, together with augmented Na reabsorption in the thick ascending part of the Henle loop, promoted by neurohormonal activation, leads to the incapacity of the kidneys to dilute urine and excrete free water [18,19]. Na delivery to the distal tubule is already reduced at this stage, but high aldosterone levels and osmotic interstitial oncotic pressures will further promote Na and water reabsorption [20].

Heart failure manifests a strong avidity for Na. Na seems to be the key player responsible for fluid redistribution and overload [21]. This hypothesis has been observed in clinical studies, which showed that increased levels of total body Na are present in patients with heart failure, both with peripheral edema and without edema, before an acute event of decompensation [22,23]. Increased Na levels are associated with increased filling pressures. Recent evidence suggests that fluid homeostasis is highly regulated by the glycosaminoglycan (GAG) network in the interstitium due to the large amount of Na bound to it, which makes it a buffer for this electrolyte [24]. The GAG network has a stronger affinity for the Na cation than other ions and molecules, thus creating a hypertonic Na microenvironment [25]. First, the excess sodium molecules are bonded to the interstitial GAG without consequent water retention or change in Na plasma concentration [26]. The entrapped Na molecules in the interstitium matrix are practically deprived of the interaction with vascular osmoreceptors, thus preventing the release of the arginine-vasopressin (AVP) hormone, which determines consequent water retention [24]. Additionally, once trapped, the interstitial Na+ cation evades the renal regulatory mechanism, significantly complicating its removal from the body [24]. This, so far, is a very potent explanation of why some patients with heart failure do not experience weight gain before acute decompensation. Eventually, due to high exposure to Na, the GAG network will lose its buffering capacity. The GAG architecture weakens and transforms, shifting from a low-compliance to a high-compliance compartment, thus facilitating fluid translocation [27]. In a dysfunctional GAG network, elevated venous pressures drive interstitial fluid transudation, surpassing the lymphatic drainage capacity and resulting in pulmonary and systemic congestion. [24]. However, an additional aspect to consider involves the endothelial glycocalyx, a vibrant glycoprotein network with vasoprotective functions [28,29]. It acts as a barrier against plasma, reduces vascular permeability, and prevents platelet and leukocyte adhesion, but most importantly, it acts as a Na buffer [29]. Mechanisms such as oxidative stress, ischemia, inflammation, excessive shear stress, increased Na concentration, and natriuretic peptides are hallmarks of heart failure and are responsible for

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endothelial glycocalyx disruption [30,31]. A damaged endothelial glycocalyx will increase vascular permeability and diminish sodium buffering capacity [32]. The loss of its buffer capacity will expose the endothelial cells to many Na cations. This, together with high aldosterone concentrations, will stimulate hyperactivation of the endothelial sodium channels from the apical region of the endothelial cells, leading to high Na uptake [33]. Therefore, impaired smooth muscle cell contraction, decreased nitric oxide (NO) production, and endothelial stiffness will occur, augmenting neurohormonal response and endothelial dysfunction [34].

The deterioration of the endothelial glycocalyx leads to elevated cardiac filling pressures and hemodynamic congestion, serving as the precursor to heart failure decompensations [21,24].

3. Does Congestion Matter in Heart Failure?

Congestion is the main cause of heart failure hospitalization and readmission and is strongly associated with heart failure prognosis [5,35,36]. In extensive clinical trials, it has been observed that the predominant cause of hospital admissions in heart failure cases is attributable to manifestations of venous congestion rather than those indicative of low cardiac output. There are several stages of congestion: hemodynamic, clinical, and systemic [3]. The first stage is hemodynamic congestion, characterized by the elevation of cardiac filling pressures and the increase in venous pressures without clinical manifestation [37,38]. Subsequently, there is organ congestion due to redistribution and accumulation of fluid within the extracellular and third space, and clinical congestion appears [37]. Hemodynamic congestion is responsible for the progression of heart failure and precedes episodes of acute heart failure decompensation [39,40]. Furthermore, persistent hemodynamic congestion despite symptom relief and aggressive diuretic therapy is a prognostic marker for rehospitalization [39,40]. This was confirmed by Ambrosy *et al.*, who showed that residual decongestion reflected by elevated natriuretic peptides before discharge is one of the strongest predictors of short-term outcomes [35]. Trials such as DOSE-AHF and CARESS-AHF have shown that nearly half of the patients hospitalized for decompensated heart failure are still not congestion-free at discharge and have higher readmission and mortality rates [41].

It is now recognized that the patient with heart failure is mainly exposed to adverse events, not during hospitalization but afterward, during the so-called "vulnerable phase" (VP) [42,43]. The VP follows an episode of acute heart failure exacerbation and lasts up to 6 months, during which patients carry a risk of readmission and mortality of 30% and 10%, respectively [42,43]. Although the factors responsible for the VP are numerous, one thing is sure. With each readmission, regardless of the precipitating factor involved in HF decompensation, there is a decline with further deterioration in cardiac function [44]. Of the numerous factors contributing to the VP pathophysiology, one seems to weigh the most: failure to relieve congestion with the persistence of increased filling pressures, ultimately leading to hemodynamic congestion, clinical congestion, and multi-organ injury [45]. A summary of biomarkers with the ability to identify the population at highest risk in this period was proposed, and these are natriuretic peptides, troponin, blood-urea-nitrogen (BUN), hematocrit and serum osmolarity [5,43,45–47]. All of these biomarkers, except for troponin, point directly or indirectly to congestion and fluid retention. Having this in mind, tackling congestion as soon as possible is crucial. There is a need to find the most sensible and specific tools for accurately detecting congestion. Non-invasive assessment of congestion has been validated in preference invasive assessment with different degrees of sensitivity and specificity [5]. The jugular venous pulse has the best sensitivity (70%) and specificity (79%) in detecting increased filling pressures and systemic congestion [4]. By using a simple composite congestion score that included (dyspnea, orthopnea, fatigue, jugular venous distension (JVD), rales, and edema), Ambrosy et al. effectively demonstrated that a subset of heart failure patients remained with residual congestion before discharge [35]. This is how the EVEREST score was born and is considered to have the most evidence-based data regarding the congestion status of the patient with AHF [35].

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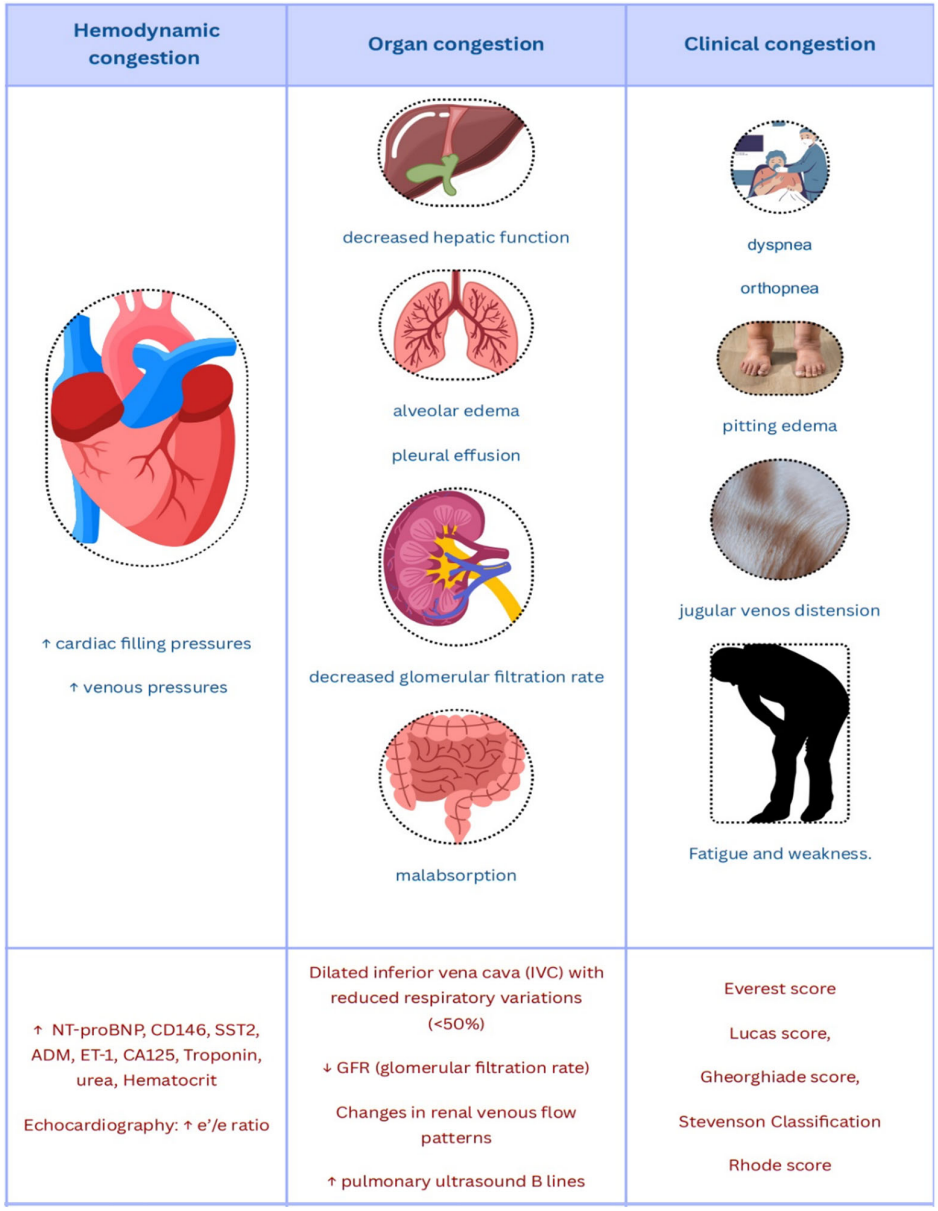

Figure 2. Overview of Hemodynamic, Organ, and Clinical Congestion with Diagnostic Tools. This figure presents a comprehensive view of hemodynamic, organ, and clinical congestion, illustrating their interrelation in congestive states. Various diagnostic tools, including biomarkers, echocardiography, lung ultrasound, vena cava dimension, and different scores for assessing congestion, are depicted surrounding each type of congestion. This visual representation elucidates the multifaceted approach to detecting and assessing congestion, highlighting the importance of integrating multiple diagnostic modalities for comprehensive evaluation and management. Abbreviations: NT-proBNP= N-terminal pro-brain natriuretic peptide. CD146= cluster of differentiation 146. SST2= Soluble suppression of tumorigenicity 2. ADM= Adrenomedullin. ET-1= Endothelin 1. CA125= cancer antigen 125.

4. Does Heart Failure Phenotype Predict Congestion Mechanism?

It has been suggested that the mechanism for the clinical manifestation of congestion (overload or redistribution) depends on the AHF phenotype. Considering that heart failure with preserved ejection fraction (HFpEF) is characterized by diastolic dysfunction and elevated blood pressures, it is more likely that the predominant clinical feature of this phenotype would be volume redistribution,

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that is, pulmonary congestion rather than volume overload. On the other hand, volume overload manifesting as systemic congestion with weight gain is associated with heart failure with reduced ejection fraction (HFrEF) phenotype, a condition characterized by both systolic and diastolic dysfunction [48].

Van Aelst et al. addressed this issue by comparing HFpEF with HFrEF patients and showed no difference in the manifestation of congestion mechanisms between the groups [49]. The study highlights that fluid redistribution and accumulation coexist [49]. Indeed, the cardiorenal continuum and hypoalbuminemia serve as robust predictors of venous congestion in heart failure. However, these features are not exclusive to a particular HF phenotype, as they are present at similar rates across all HF phenotypes [50,51]. However, a missing link remains that should elucidate the diverse manifestations of congestion in all HF models, irrespective of ejection fraction. As is often the case in daily practice, the answer may be correct in front of us, and this is indeed the case with our elusive missing link concerning congestion manifestation. If we look back at the 1971 Framingham Criteria introduced by McKee *et al.*, two primary criteria for defining congestive heart failure were jugular venous distension and hepato-jugular reflux. Not only do they have a high specificity for congestive heart failure, but they are associated with elevated proper atrial pressures and right ventricular (RV) dysfunction [52,53].

The elusive factor, consistently present and described across all HF phenotypes, capable of predicting congestion, may indeed be RV dysfunction [54]. It carries a poor prognosis in patients with heart failure regardless of ejection fraction [54]. RV dysfunction/failure is responsible for increased central venous pressures and consequent systemic congestion. Still, recently, it has been pointed out that RV dysfunction and RV-Pulmonary artery uncoupling are associated with pulmonary congestion [55]. Kobayashi et al. showed that in patients with acute decompensated heart failure, a low tricuspid annular plane systolic excursion (TAPSE) and TAPSE/PSAP (pulmonary artery systolic pressure) ratio correlate with an increased number of B lines detected by lung ultrasound upon admission and at discharge [55]. Other studies showed that chronic heart failure with RV dysfunction and RV–PA (pulmonary artery) uncoupling correlated with subclinical pulmonary and peripheral congestion and had a worse prognosis [56]. This might be explained by decreased fluid drainage from the interstitial lung tissue via pulmonary lymphatics due to elevated right atrial pressures. Assessing RV function and early recognition of RV dysfunction is crucial for managing patients with acute and chronic heart failure and thus improving prognosis.

5. Clinical and Paraclinical Integrative Assessment of Congestion

5.1. Clinical Congestion Scores

Physical assessment is not accurate enough in detecting low congestion levels. More than 50% of patients discharged from the hospital have residual congestion with high levels of natriuretic peptides [41].

Relying only on clinical signs has a low sensitivity and a poor predictive value in identifying decompensated HF, which is why congestion scores and biomarkers are important tools [5,57].

Several scores have been tested and proposed to quantify congestion: the Lucas score, Gheorghiade score, Stevenson Classification, Rhode score, and Everest score [5]. All of these scores combine several clinical and paraclinical indicators such as orthopnea, jugular venous distension, rales, edema, hepatomegaly, third heart sound, the dose of diuretics, fatigue, orthostatic testing, 6-minute walk test, N-terminal pro-brain natriuretic peptide (NT-proBNP) [35,57]. Although there is a high confidence level in determining congestion by using these scores, there is still a lack of data for their use in routine clinical practice, as they served so far more as a predictive tool than a management tool. However, emerging evidence points to the EVEREST score as a strong candidate for routine congestion management in acute heart failure [5,35].

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5.2. The New Congestion Biomarkers on the Horizon

When it comes to biomarkers, natriuretic peptides have been extensively studied for congestion in heart failure, and their role in diagnosis and prognosis is well established in current guidelines [58].

However, their utility is restricted due to the failure of natriuretic peptides to demonstrate any advantage in guiding decongestion therapy compared to standard care. This is further complicated because they can be elevated in ischemia or atrial fibrillation situations, which may not necessarily indicate congestion [59–61]. Another pitfall is that natriuretic peptides fail to show the actual contribution of right-sided heart failure to the clinical congestion picture [62]. Thus, despite their evident utility, natriuretic peptides should be integrated with other clinical and paraclinical parameters to predict and manage congestion.

Another interesting congestion biomarker extensively studied recently in patients with congestive heart failure is Carbohydrate antigen 125 (CA125), a glycoprotein expressed on serosal epithelial cells. Even though it's validated as a marker for ovarian cancer, it is highly expressed in conditions associated with volume overload, such as heart failure, renal failure, or liver failure [63]. Overexpression of CA125 has been suggested to be a consequence of mechanical stress induced by elevated hydrostatic pressure [64]. Several studies have demonstrated the association of CA125 with systemic congestion in patients with acute decompensated heart failure [62,64,65]. However, recent studies have revealed that the utility of CA125 extends beyond its role as a congestion marker. It has been demonstrated to predict both short and long-term outcomes in decompensated heart failure, suggesting its potential to guide diuretic therapy [66,67]. However, some aspects regarding CA 125 use in heart failure need to be correctly comprehended.

Firstly, since its release is primarily associated with third-space fluid accumulation, it appears ineffective in identifying patients with acute-onset conditions characterized by predominant interstitial pulmonary congestion. Secondly, compared to natriuretic peptides, it has a longer half-life, up to 12 days, and is not influenced by confounders such as age or kidney function [64]. On the other hand, these features present some advantages: CA 125 could detect patients with RV failure and chronic fluid overload, thereby impacting escalation of decongestive therapy, and better management of HFpEF patients with associated comorbidities [64,68].

A new marker of congestion in heart failure that has recently emerged is CD146 (Cluster of differentiation 146), a glycoprotein highly expressed at the junctions of endothelial cells throughout the human vascular system, smooth muscle cells, and pericytes [67]. It is an adhesion molecule active in venous integrity [68,69]. It is overexpressed and released into the bloodstream in conditions associated with endothelial dysfunction, vascular injury, or mechanical vascular stretch [70]. Different roles of CD146 have been described: angiogenesis, vessel permeability, and leukocyte transmigration [71,72]. Increased levels of CD146 have been linked to peripheral venous congestion in chronic heart failure due to endothelial damage and disruption [68,70]. It has been associated with poor outcomes in patients with heart failure and reduced ejection fraction [73]. In one prospective study by Jukneviciene et al. on patients with acute dyspnoea admitted to the emergency department, CD146 strongly correlated with the degree of vascular and tissue congestion assessed imagistically regardless of the NT-proBNP levels [74]. Although a promising biomarker, it must be further validated in studies with different heart failure clinical scenarios.

Another peptide involved in maintaining vascular integrity by barrier stabilization of the endothelial cells is adrenomedullin (ADM), which has been proposed as a potential biomarker for congestion in patients with heart failure [75–77]. In additional studies involving patients hospitalized for acute heart failure (AHF), ADM levels exhibited a significant association with both clinical congestion upon admission and residual congestion before discharge [77,78]. Furthermore, various other investigations have demonstrated a correlation between ADM levels and clinical congestion, as well as with mean pulmonary artery pressure and pulmonary capillary wedge pressure [79].

The ST2 (suppression of tumorigenicity 2) protein is significantly associated with heart failure. Elevated levels of sST2 have been observed in the bloodstream of heart failure patients compared to healthy individuals [80]. ST2 is involved in the pathophysiology of heart failure, particularly in

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promoting myocardial fibrosis and ventricular remodeling. Additionally, it serves as a valuable biomarker for prognosis and risk stratification in patients with heart failure [81,82]. Monitoring sST2 levels can provide valuable information for managing and predicting outcomes, as sST2 positively correlates with echocardiographic indicators of right-sided heart failure and invasively measured central venous pressure in patients with acute heart failure. Furthermore, sST2 is a surrogate marker of diuretic resistance for heart failure patients with renal dysfunction at presentation [83–85]. It is also associated with an increased risk of mortality and hospitalization [86,87].

Endothelin-1 (ET-1) is a potent vasoconstrictor with additional anti natriuretic and mitogenic properties [68]. It plays a crucial role in modulating salt and water homeostasis and maintaining vascular tone and blood pressure in healthy individuals. Furthermore, ET-1 contributes to inflammation and neurohormonal activation. Elevated ET-1 levels increase peripheral vascular resistance, exacerbating hypertension and impairing cardiac function [88,89]. In patients with heart failure with preserved ejection fraction (HFpEF), circulating levels of ET-1 are higher and strongly correlated with mean pulmonary artery pressure and pulmonary capillary wedge pressure [90,91]. ET-1 has been investigated both as a predictor of heart failure and as a prognostic marker in patients with established acute or chronic congestive heart failure. Higher baseline ET-1 concentrations are independently associated with worse clinical outcomes and a more rapid decline in kidney function. Notably, treatment with dapagliflozin has shown benefits across a range of ET-1 concentrations, leading to a modest decrease in serum ET-1 concentration [92].

Although these emerging congestion biomarkers are very promising, some still need validation. On the other hand, several other markers commonly encountered in daily practice can be used to estimate congestion, such as hemoglobin, hematocrit, blood urea nitrogen, serum protein, and liver enzymes [4,5,69,93,94]. For example, by using hemoglobin and hematocrit, one can easily assess the change in plasma volume through the Duarte formula [95]. A threshold of > 5.5 ml/g for the estimated plasma volume has been linked to excessive volume overload and poor outcomes [96]. Another useful parameter is the increase in creatinine level during diuretic therapy, which indicates hemoconcentration through successful decongestion rather than worsening renal function [68,97].

5.3. Imaging Methods for Assessing Congestion

When considering the visual assessment of congestion, the most powerful imaging tool in evaluating congestion starting from the pre-hospital setting to the emergency department, in-hospital, and ambulatory ward is ultrasonography (lung ultrasound and abdominal inferior vena cava measurement) [5]. With lung ultrasound, rapid determination of B-lines (ultrasound lung comets “comet tail“ -like) at the patient’s bedside is possible. The number of B-lines is proportional to congestion severity, with good sensitivity and specificity [98]. Lung ultrasound can assess residual pulmonary congestion pre-discharge and is considered a strong predictor of adverse outcomes post-discharge [99]. Dilated inferior vena cava (IVC) with reduced respiratory variations (<50%) is a strong predictor of elevated right atrial pressures and systemic congestion [100,101].

Renal Doppler venous flow offers valuable insights into the hemodynamic status and renal function, particularly in patients with congestive heart failure. Changes in renal venous flow patterns can transition from a continuous to a discontinuous pattern, indicating alterations in renal perfusion and congestion [102,103].

6. Congestion Management: Diuretics the Sole Remedy for Congestion Relief?

The primary focus of therapy for HFrEF and HFpEF is decongestion, given their comparable clinical profiles of congestion during acute heart failure decompensation. The significant correlation between early administration of intravenous (IV) loop diuretics and reduced in-hospital mortality underscores the endorsement of this approach as first-line therapy in AHF. (class I, level of evidence B) [58]. Early initiation of loop diuretics improves dyspnea substantially within 6 hours. The main mechanism of action is renal natriuresis and diuresis. The diuretic response is influenced by factors such as the type and dosage of diuretic, extent of volume overload, body composition, and kidney function. Indicators of good response to diuretics are weight loss, fluid output, and urinary sodium

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[4]. The absence of clinical congestion and the lack of signs or symptoms, including dyspnea at discharge, are deemed inadequate predictors for achieving complete decongestion. Thus, patients still experience high rates of hospital readmissions, with only one-third remaining congestion-free at 60 days [39,41]. High levels of natriuretic peptides at discharge, despite symptom relief, indicate treatment failure and are considered one of the most robust predictors of mortality [104]. This underscores the lack of correlation between weight loss and decongestion [3,35].

The main goal for patients admitted with acute decompensated heart failure is to prevent residual decongestion. To do so, one must thoroughly assess the patient on admission for possible features that might lead to residual congestion. For example, it is important to distinguish from the beginning what the mechanism responsible for congestion is: volume overload or redistribution. Also, the presence of kidney impairment, liver failure, hypoproteinemia, increased intra-abdominal pressure, and low blood pressure may alter the diuretic response and impede decongestion. Urinary output, urinary ionogram, weight change, NTproBNP monitoring, and congestion scores are all helpful tools in monitoring decongestion response and thus guiding dose escalation of loop diuretics or bail-out therapy through ultrafiltration [4,35,97,105]. Chronic use of loop diuretics in patients with chronic heart failure might lead to diuretic resistance, impeding decongestion in case of a decompensation episode [106]. This phenomenon is explained by the diuretic-induced hypertrophy of the distal tubular renal cells, which causes compensatory sodium reabsorption and, thus, a reduction in natriuresis [107].

According to the position statement of the Heart Failure Association of the European Society of Cardiology (HFA ESC) [4], one efficient way to tackle residual decongestion is to evaluate early diuretic response in case of an episode of acute heart failure. This is done by determining urinary output and measuring urinary sodium excretion at 2 hours from the initial dose of loop diuretics. If a urinary spot sodium < 50-70 mEq is measured at 2 hours, and the urinary output is less than 150 ml per hour, then it is safe to say that there is an insufficient diuretic response, and doubling the dose of IV loop diuretics should be considered [4]. Certainly, this process continues until the maximum dose is reached if natriuresis and urinary output remain insufficient. However, one should remember that loop diuretics should be administered in a protein-bound form and dosed based on protein plasma levels for adequate secretion in the proximal tubule.

Diminished plasma protein levels resulting from chronic loss or reduced production impede plasma refill from the interstitium and, thus, delivery of loop diuretics to the kidney [108]. In this condition, escalating the loop diuretic dose before correction of hypoproteinemia is futile. Another aspect that needs to be taken into consideration when tackling residual decongestion, especially in patients with advanced heart failure, is hypochloremia. Hypochloremia is a marker of bad prognosis, promotes sodium retention, and is associated with diuretic resistance [109]. This was first observed in the 1950s by Rubin Albert *et al.*, who found that patients undergoing treatment with mercurial diuretics experienced hypochloremia and diuretic resistance. However, this resistance was successfully addressed by administering exogenous lysine chloride, restoring the diuretic response [110]. Low chloride (Cl) levels stimulate renin secretion and the up-regulation of NaCl channels in the distal tubule, thus increasing sodium reabsorption [111]. These mechanism insights led to administering hypertonic saline with loop diuretics to augment diuresis [112,113]. Theoretically, lone hypertonic saline can restore low chloride levels, prevent sodium retention, osmotically shift fluid into the intravascular compartment, and temporarily reduce neurohormonal activation and thus improve diuresis [114]. However, a potential issue arises due to tubuloglomerular feedback, which could eventually decrease renal blood flow [114]. This can be overcome with the concomitant administration of furosemide, thus potentiating diuresis. This was tested in several studies, where hypertonic saline was administered alongside high-dose intravenous furosemide, as opposed to standard therapy, in patients with acute decompensated heart failure [112,113]. The results were a higher effective diuresis, shorter hospital stay, symptom improvement, and reduced hospital readmission [112,113]. Further randomized controlled studies are required to elucidate and validate this therapeutic regimen. Nevertheless, it is an option for patients who have not responded to conventional therapies and are hyponatremic.

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Checking plasma and urinary electrolytes, urinary output, plasma, and urinary proteins should be done as soon as possible in the early phase of the admission as it could impact diuretic response and avoid residual decongestion. An essential matter that needs to be assessed starting from admission is whether we are dealing with congestion due to volume overload or fluid redistribution. As mentioned earlier, more than half of heart failure patients exhibit little or no change in body weight before admission, and these are likely to experience fluid redistribution. It is unwise to try escalating diuretic doses in these patients because it can only further decrease plasma volume, reduce renal blood flow, enhance neurohormonal activation, and worsen renal failure. The main goal in this population is to improve venous capacitance and reduce cardiac filling pressures [58]. This can be achieved by adding vasodilators to low doses of diuretics, as it can reduce preload and induce arterial vasodilation [115].

Achieving decongestion can be challenging in certain cases, particularly when hindered by factors like hypotension, severe systolic dysfunction, or severe pulmonary hypertension. Consequently, the utilization of inotropic agents or heart rate reduction may be warranted to overcome these challenges. Numerous pharmacological agents are being tested to improve pulmonary capillary wedge pressure or venous capacitance, but besides symptomatology, they have failed to improve outcomes [115]. If the patient is hemodynamically stable, early introduction of neurohormonal blockers such as Angiotensin Receptor-Neprilysin Inhibitor (ARNi), Sodium-glucose co-transporter two inhibitors (iSGLT), Mineralocorticoid Receptor Antagonists (MRA), and beta-blockers might reduce cardiac filling pressures, and improve venous capacitance and fluid redistribution [58]. This strategy has been tested in the STRONG-HF trial. An intensive treatment strategy of rapid up-titration of guideline-directed medication (at least two neurohormonal blockers) in stable hospitalized patients can overcome residual decongestion and improve outcomes [116].

Diuretic resistance due to distal tubule sodium avidity can be overcome by using thiazide or thiazide-like diuretics. These agents block the sodium-chloride cotransporter from the distal tubule, promoting natriuresis and kaliuresis [117,118]. They enhance diuresis when used in combination with loop diuretics. However, there are some major pitfalls when using these agents: they cannot dilute urine, necessitate protein binding for tubular secretion, and are independent predictors of hyponatremia and hypokalemia, correlating with increased all-cause mortality [118,119]. Thiazide-induced hypokalemia may be counteracted by using mineralocorticoid receptor blockers. Mineralocorticoid antagonists, due to their anti-neurohormonal activity, can prevent congestion, but otherwise, they are not useful for decongestion therapy in an acute setting. The ATHENA-HF trial failed to show the superiority of high-dose spironolactone compared to the lowest dose in reducing NT-proBNP and increasing urinary output in patients with decompensated heart failure [120,121].

Acetazolamide is a tempting, new, otherwise old agent used to facilitate congestion in patients with decompensated heart failure. It is a carbonic anhydrase inhibitor that facilitates sodium reabsorption in the proximal tubule, formally known for treating altitude pulmonary edema and glaucoma [3,4]. As 65% of sodium is absorbed in the proximal tubule, inhibiting its absorption at this stage through the carbonic anhydrase inhibitor will lead to increased natriuresis and enhanced delivery of chloride to the macula densa, resulting in reduced neurohormonal activity [16]. It is only logical to use this agent to enhance diuresis and decongestion to achieve euvolemia. Acetazolamide was evaluated in the ADVOR study conducted by Mullens et al., involving 519 patients with acute decompensated heart failure. The study demonstrated that adding acetazolamide to loop diuretics in these patients led to more effective decongestion, with impacts and side effects comparable to those observed in the placebo group [106]. However, there are some drawbacks to this strategy. The addition of intravascular acetazolamide to IV furosemide, aimed at achieving more efficient decongestion, did not result in a reduction of all-cause mortality or rehospitalization for heart failure, which remained similar between groups (29% vs 27%) [122,123]. Despite observing a greater increase in natriuresis and urinary output in patients with a glomerular filtration rate (GFR) < 40 ml/min/m2 from the acetazolamide group, this was offset by a higher incidence of worsening renal function. Whether this primarily indicates positive clinical decongestion or represents an early sign of acute kidney injury [122,123]. Overall, the adage of “better sooner than later” does not seem to apply to the

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prognosis of heart failure with this drug, necessitating further investigation through additional studies.

The new kid on the block that revolutionized treatment in patients with chronic heart failure in recent years regarding survival and rehospitalization was SGLT2 inhibitors [124,125]. Numerous proposed mechanisms were responsible for their beneficial effects, one of them being natriuresis, which led clinicians to test this drug in patients with acute heart failure in addition to loop diuretics to increase diuresis, relieve congestion, and prevent residual decongestion [126]. The biggest trial to test SGLT2 inhibitors in acute heart failure was the EMPULSE trial, where patients were assigned to receive empagliflozin 10 mg daily or placebo [127]. The trial concluded that initiating empagliflozin in patients with acute heart failure is safe and well-tolerated regardless of ejection fraction and resulted in a clinical benefit at 90 days follow-up in terms of all-cause mortality and time to first heart failure event [127]. However, it's important to note that the treatment was randomized at a median time of three days from hospitalization when patients were considered stable [127]. Thus came the DICTATE-HF trial, where researchers tested the diuretic efficacy of SGLTi when initiated within 24 hours of hospital admission in patients with acute heart failure. The study failed to show a statistical improvement in diuretic response at five days and discharge for dapagliflozin compared to standard usual care [112]. The effectiveness of SGLTi as a diuretic regime in addition to standard decongestive therapy in patients with acute decompensated heart failure was tested in the EMPAG-HF randomized study [129]. The study has shown that empagliflozin-treated patients, compared to those with standard treatment, experienced a 25% increase in 5-day urine output without kidney injury and a greater decline in natriuretic peptide levels [129]. Conversely, the EMPAG-HF study underscored the effectiveness of SGLT2 inhibitors as adjunctive diuretic therapy alongside standard decongestive treatment in patients with acute heart failure. Results indicated that patients treated with empagliflozin experienced a 25% increase in 5-day urine output without kidney injury and a more significant reduction in natriuretic peptide levels than those receiving standard care [129].

In summary, the usage of SGLT2 inhibitors in acute heart failure is not well established, particularly in alleviating congestion. Potential risks, such as ketoacidosis or acute kidney injury, need to be carefully considered, especially during the "acute vulnerable phase" characterized by elevated lactate or inflammatory levels, hemodynamic instability, or low blood pressure [130,131]. Nonetheless, initiating SGLT2 inhibitors early during heart failure admission offers advantages regarding short-term outcomes and tackling residual congestion.

7. Conclusions

Gaining insight into the pathophysiology and clinical presentation of congestion is essential for improving the management of heart failure patients. Utilizing straightforward tools like pulmonary echocardiographic parameters assessing cardiac filling pressure or circulating serum congestion biomarkers, clinicians can anticipate future episodes of congestion decompensation or identify residual congestion following an acute heart failure episode. This multiparametric approach for assessing congestion might be especially beneficial for monitoring and guiding decongestive therapies.

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