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Review

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Review

The Congestion "Pandemic" in Acute Heart Failure Patients

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Abstract: Congestion is not only considered a cardinal sign of heart failure but also the main mechanism responsible for heart failure decompensation episodes. It is now accepted that congestion determines the phenotype of heart failure presentation in the acute setting either by volume overload, volume maldistribution or both. Recognizing the mechanism responsible for congestion is paramount, as it implies that different therapeutic strategies are required to achieve decongestion. Although achieving complete decongestion is considered the target, in most cases of acute heart failure episodes, this is hampered by various factors that lead up to residual congestion which is considered one of the strongest predictors of future cardiovascular events and poor outcomes. In this review, by immerging into the pathophysiology mechanisms of congestion, unraveling its phenotypes and discussing new diagnostic tools for targeting therapy, we are trying to acknowledge the importance of "the congestion phenomenon" and its scale among heart failure patients which is of pandemic proportions.

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

1. Introduction - Understanding congestion

It has been two years since the end of the SARS-COV-2 pandemic, a global health burden that is responsible for nearly 3.4% of deaths on a global scale, yet another one is lurking from some time now, affecting nearly 64.3 million people worldwide with 1-year mortality rates ranging from 21-36% [1,2]. As it happens, we are talking about heart failure (HF), a rapidly growing public health burden of pandemic proportions. 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/functional abnormality associated with elevated natriuretic peptide levels and evidence of pulmonary or systemic congestion [3].

Congestion is more than clinical signs and symptoms, and it seems to be the key-player underlying the complex pathophysiology of heart failure syndrome [4]. Congestion is clinically expressed into signs and symptoms due to extracellular fluid accumulation, as a result of the increase in left-sided cardiac filling pressures [4,5]. The increase of cardiac filling pressures is an early indicator of hemodynamic congestion which precedes the development of congestive symptoms by days or weeks [6]. Congestion leads to heart failure decompensation which manifests clinically with dyspnea, orthopnea, systemic edema, jugular venous distention and third heart sound [4,6]. It is important to understand the underlying mechanism that leads first to hemodynamic congestion and then to clinical congestion, which is why early recognition and proper treatment of this condition is imperative. To do so, one first needs to identify the transition phase between hemodynamic congestion and clinical congestion.

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Congestion is a consequence of both forward and backward failure of the heart with the inability of the compensatory adaptive mechanism to counter the negative effects of low oxygen delivery to the peripheral tissues [7]. Reduced cardiac output, with diminished renal perfusion, results in activation of the renin-angiotensin-aldosterone system, the arginine-vasopressin system, sympathetic nervous system, with sodium and water accumulation and consequent volume overload [7]. The retained sodium (Na) is stored mostly in the extracellular compartment, mainly in the interstitium 65%, and 25% in the intravascular compartment [8].

2. Importance of congestion in heart failure

Congestion is the main cause of heart failure hospitalization and readmissionandis strongly associated with heart failure prognosis [6,9,10]. In large trials, we see that most heart failure admissions occur due to signs and symptoms of venous congestion rather than those of low cardiac output [9,11]. There are several different stages of congestion: hemodynamic congestion, clinical congestion and systemic congestion [4]. The first stage is hemodynamic congestion which is characterized by the increase in venous pressures and elevation of cardiac filling pressures without clinical manifestation [11,12]. Subsequently, there is organ congestion due to redistribution and accumulation of fluid within extracellular and third space and finally the appearance of clinical congestion [11].

Hemodynamic congestion is responsible for the progression of heart failure and precedes episodes of acute heart failure decompensation [13,14]. Not only this, but persistent hemodynamic congestion despite symptom relief and aggressive diuretic therapy is a prognostic marker for rehospitalization [13,14]. This was tested by Ambrosy *et al* who showed that residual congestion reflected by elevated natriuretic peptides before discharge is one of the strongest predictors of short-term outcomes [9]. 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 [15].

It is now recognized that the heart failure patient is mostly exposed to adverse events not during hospitalization but afterwards, during the so-called "vulnerable phase" (VP) [16,17]. The VP follows an episode of acute heart failure (AHF) exacerbation and lasts up to 6 months during which patients carry a risk of readmission and mortality of 30% and 10% respectively [16,17]. Although the factors responsible for the VP are numerous, one thing is certain: with each readmission, no matter what decompensation factor is involved, there is a decline with further deterioration in cardiac function [18]. Of the numerous contributing factors for the "VP" pathophysiology one seems to weigh the most: failure to relieve congestion with the persistence of increased filling pressures which ultimately leads to hemodynamic congestion, symptomatic congestion and multi-organ injury [19]. A summary of biomarkers with the ability to identify the population at highest risk in this period was proposed and these are natriuretic peptides (NTproBNP), troponin, blood-urea-nitrogen (BUN), hematocrit and serum osmolarity [6]. 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, thus the need to find the most sensible and specific tools in detecting congestion with accuracy. Non-invasive assessment of congestion has been validated in favor of invasive assessment with different degrees of sensitivity and specificity [6]. The jugular venous pulse has the best sensitivity (70%) and specificity (79%) in detecting increased filling pressures and systemic congestion [5]. By using a simple clinical composite congestion score that included orthopnea, jugular venous distention and peripheral edema, Ambrosy *et al* managed to show a significant proportion of heart failure patients with residual congestion before discharge [9]. This is how the EVEREST score was born and is considered to have the most evidence-based data regarding the congestion status of the AHF patient [9].

3. Volume overload or volume distribution?

Congestion is the cardinal manifestation of both chronic heart failure (CHF) and AHF. The main mechanisms responsible for venous congestion are volume redistribution and volume overload. The

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first mechanism describes the rapid distribution of blood volume from systemic circulation to pulmonary venous circulation and is due to a reduction in the capacitance of the splanchnic venous bed [20]. 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 [21–23]. 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, increased preload and afterload [24]. Fluid shifts between the interstitial and intravascular compartments occur weeks before the acute event. This happens mostly without any weight change and is characterized by increased cardiac filling pressures and capillary wedge pressures, the driving mechanism being hyperstimulation of the adrenergic receptors in splanchnic veins [24]. This rather silent mechanism expands intravascular volume 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 [25].

The second mechanism responsible for congestion is volume overload, a rather insidious process in which there is an absolute increase in water and sodium body content [26]. Volume overload is more common in those with cardio-renal dysfunction and chronic heart failure [26]. Venous distension in turn augments endothelial dysfunction and sympathetic activation which will further promote the fall in splanchnic venous capacitance and consequent fluid redistribution [27]. In other words, there is an overlap between these two mechanisms. Fluid retention is caused by impaired renal sodium excretion [26]. The heart-kidney cross-talk is very important to understand as Na homeostasis, neurohormonal activation and inflammation impair nephron tubular flow which contributes to Na and water retention [28]. This will lead to an increase in central venous pressure and intra-abdominal pressure that further worsens renal function [29]. Most Na reabsorption takes place in the proximal renal tubule (65%) mediated by Na transporters and Na/K ATP-ase [30]. As Na is reabsorbed, water passively followsby 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 inthe proximal tubule by the increase of peritubular oncotic pressure, renal venous pressures, and renal lymph flow [29]. Not only this, but 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 [29]. This, together with augmented Na reabsorption in the thick ascending part of the Henle loop which is promoted by neurohormonal activation leads to the incapacity of the kidneys to dilute urine and excrete free water [30,31]. By now, Na delivery to the distal tubule is already reduced, but high aldosterone levels and osmotic interstitial oncotic pressures will further promote Na and water reabsorption [32].

It can be noted that heart failure manifests a strong avidity for Na. Na seems to be the key player responsible for fluid redistribution and overload [33]. This hypothesis has been observed in clinical studies which showed that increased levels of total body Na are present in heart failure patients with peripheral edema and without edema before an acute event of decompensation [34,35].

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 [36]. The GAG network has a stronger affinity for the Na cation in comparison to other ions and molecules, thus creating a hypertonic Na microenvironment [37]. Because the interstitium is abundant in GAG, it can bond a great deal of Na, especially if in excess (which is the case of heart failure) without consequent water retention or change in Na plasma concentration [38]. Once Na is trapped in the interstitium matrix, the vascular osmoreceptors are practically deprived from interaction with it, thus preventing the release of arginine-vasopressin (AVP) hormone and

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consequent water retention [36]. Also, the trapped interstitial Na cation escapes the renal regulatory mechanism, making it very hard to remove from the body [36]. This so far, is a very potent explanation of why some heart failure patients 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 alters, transforming from a low compliance to a high compliance compartment facilitating fluid translocation [39]. In the context of a dysfunctional GAG network, elevated venous pressures determine interstitial fluid transudation that exceeds the lymphatic drainage capacity, leading to pulmonary and systemic congestion [36]. But there is more to the story and it involves the endothelial glycocalyx which is a highly rich glycoprotein network with vasoprotective functions [40,41]. It acts as a shield against plasma, reduces vascular permeability, and prevents platelet and leukocyte adhesion, but most importantly it acts as a Na buffer [41]. Mechanisms such as oxidative stress, ischemia, inflammation, excessive shear stress, increased Na concentration, and natriuretic peptides are hallmarks of heart failure and responsible for endothelial glycocalyx disruption [42,43]. A damaged endothelial glycocalyx will lead to increased vascular permeability and diminished sodium buffering capacity [44]. The loss of its buffer capacity will expose the endothelial cells to a great deal of 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 [45]. Therefore, impaired smooth muscle cell contraction, decreased nitric-oxide (NO) production and endothelial stiffness will occur, augmenting neurohormonal response and endothelial dysfunction [46].

Damaged endothelial glycocalyx is responsible for increased cardiac filling pressures and hemodynamic congestion, the precursor to heart failure decompensations [33,36].

4. Does heart failure phenotype predict congestion mechanism?

It has been suggested that the mechanism for the clinical manifestation of congestion (overload or redistribution) is dependent on the AHF phenotype. Taking into consideration 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, 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 [47].

Van Aelst *et al* addressed this particular issue by comparing HFpEF with HFrEF patients and showed that there was no difference when it comes to congestion mechanism manifestation between the groups [48]. The study highlights that fluid redistribution and fluid accumulation can coexist [48]. Of course, cardio-renal continuum and hypoalbuminemia are strong predictors for venous congestion in heart failure but these features are not specific to a certain HF phenotype as they can be traced in similar rates in all HF phenotypes [49,50]. Still, there is a missing link that should explain the various congestion manifestations in all HF models independently of ejection fraction. As it so often happens in daily routine sometimes the answer is right in front of us and this seems to be the case with our missing link regarding congestion manifestation. If we look back on the 1971 Framingham Criteria introduced by McKee *et al*, two of the major criteria for defining congestive heart failure were jugular vein distension and hepato-jugular reflux. Not only do they have a high specificity for congestive heart failure but they are associated with elevated right atrial pressures and right ventricle (RV) dysfunction [51,52]. The missing link, the one thing that can be found in all HF phenotypes and is able to predict congestion is RV dysfunction [53]. It carries a poor prognosis in heart failure patients regardless of ejection fraction [53]. RV dysfunction/failure is responsible for increased central venous pressures and consequent systemic congestion but recently it has been pointed out that RV dysfunction and RV-Pulmonary artery uncoupling are associated with pulmonary congestion [54]. Kobayashi *et al* demonstrated that a low TAPSE and TAPSE/PSAP ratio are associated with a higher number of B lines assessed by lung ultrasound on admission and at discharge in patients with acute decompensated heart failure [54]. Other studies showed that chronic

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heart failure with RV dysfunction and RV–PA uncoupling correlated with subclinical pulmonary and peripheral congestion and had a worse prognosis [55]. This might be explained by the decreased drainage of the fluid 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 acute and chronic heart failure patients and thus improving prognosis.

5. Assessing congestion: new biomarkers on the horizon and the utility of congestion scores)

Physical assessment is not accurate enough in detecting low levels of congestion. More than 50% of patients discharged from the hospital have residual congestion with high levels of natriuretic peptides [15].

Relying only on clinical signs, has a low sensibility and a poor predictive value in identifying decompensated HF, which is why congestion scores and biomarkers are important tools [6,56].

Several scores have been tested and proposed to quantify congestion and these are the Lucas score, Gheorghiade score, Stevenson Classification, Rhode score, and Everest score. All of these scores combine several clinical indicators such as orthopnea, jugular vein distension, rales, edema, hepatomegaly, third heart sound, the dose of diuretics, fatigue, orthostatic standing, 6 minutes walk test, NTProBNP [9,56]. Although there is a high confidence level in determining congestion by the use of these scores , there is still lack of data for their use in routine clinical practice, as they served so far more as a predictive tool rather than a management tool. However, there is emerging evidence that points to the EVEREST score as a strong candidate for routine congestion management in acute heart failure [6,9].

When it comes to biomarkers, natriuretic peptides (NTproBNP) are the most studied for congestion in heart failure and their role in diagnosis and prognosis is well established in current guidelines [57]. However, their use is limited because natriuretic peptides failed to show any benefit for guiding decongestion therapy compared to standard care, confounded by the fact that they can be highly expressed in situations of ischemia or atrial fibrillation which does not necessarily imply congestion [58–60]. Another pitfall is that natriuretic peptides fail to show the real contribution of right-sided heart failure to the clinical congestion picture [61]. Thus, natriuretic peptides, despite their evident utility, should be integrated with other clinical and paraclinical parameters to predict and overcome congestion.

Another interesting congestion biomarker that has been extensively studied in recent years in patients with congestive heart failure is Carbohydrate antigen 125 (CA125), a glycoprotein expressed on serosal epithelium 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 [62]. Overexpression of CA125 has been suggested to be a consequence of mechanical stress induced by elevated hydrostatic pressure [63]. Several studies have demonstrated the association of CA125 with systemic congestion in patients with acute decompensated heart failure [61,63,64]. However, the utility of CA125 goes beyond being a congestion marker according to recent studies and has been proven to be predictive for short and long-term outcomes in decompensated heart failure, thus it has a potential use to guide diuretic therapy [65,66]. However, there are some aspects regarding CA 125 use in heart failure that need to be properly understood: Firstly, because its release is mostly related to third space fluid accumulation, it does not seem to identify patients with acute-onset where there is the predominance of interstitial pulmonary congestion.Secondly, in comparison 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 [63]. On the other hand, these features can present some advantages: for example, CA 125 might identify heart failure patients with chronic and long-lasting fluid overload or RV failure and therefore impact escalation of decongestive therapy; another advantage might be better management of HFpEF patients with associated comorbidities [63,67].

A new marker for 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 with an active role in venous integrity [67,68]. It is overexpressed and released into the bloodstream in

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conditions associated with endothelial dysfunction vascular injury or mechanical vascular stretch [69]. Different roles of CD146 have been described: angiogenesis, vessel permeability and leukocyte transmigration [70,71]. Increased levels of CD146 have been linked to peripheral venous congestion in chronic heart failure due to endothelial damage and disruption [67,69]. It has been associated with poor outcomes in patients with heart failure and reduced ejection fraction [72]. 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 NTproBNP levels [73]. Although a promising biomarker, it needs to 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 clinical congestion in heart failure patients [73–75]. In a study on patients hospitalized for AHF, ADM levels were strongly associated with clinical congestion at admission and residual congestion before discharge [75,76]. In other several studies, ADM has been shown to correlate with clinical congestion, mean pulmonary artery pressure, and pulmonary capillary wedge pressure [77].

Although these emerging congestion biomarkers are very promising, some of them still need validation. On the other hand, there are several other markers commonly encountered in daily practice that can be used to estimate congestion, such as hemoglobin, hematocrit, blood urea nitrogen, serum protein, and liver enzymes [68,78,79]. For example, by using hemoglobin and hematocrit, one can easily assess through the Duarte formula the change in plasma volume [80]. The estimated plasma volume has been linked with an excessive volume overload and poor outcome by using a threshold > 5.5 ml/g [81]. Another useful parameter is the increase in creatinine level during diuretic therapy which rather points out hemoconcentration through successful decongestion rather than worsening renal function [67,82].

Dilated IVC with reduced respiratory variations (<50%) is a strong predictor of elevated right atrial pressures and systemic congestion [85,86]. When it comes to imagistically assessing 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) [6]. With lung ultrasound, rapid determination of B-lines (“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 [83]. Lung ultrasound can be used to assess residual pulmonary congestion pre-discharge and is considered a strong predictor of adverse outcomes post-discharge [84].

6. Diuretics, sole solution for congestion relief? How to overcome residual congestion and diuretic – resistance?

Decongestion is the main target for therapy, both for HFrEF and HFpEF, due to their similar clinical profile of congestion in acute heart failure decompensation. The strong association of early treatment with IV loop diuretics with lower in-hospital mortality supports this recommendation as first line therapy in AHF (class I, level of evidence B) [57]. 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 the dose of diuretic, type, degree of volume overload, body composition and kidney function. Indicators of good response to diuretics are weight loss, fluid output and urinary sodium [5].

The lack of clinical congestion and the absence of signs or symptoms, including dyspnea at discharge, are considered a poor predictor for complete decongestion. Thus, patients still experience high rates of hospital readmissions with only one third of them remaining congestion free at 60 days [13,15].

High levels of natriuretic peptides at discharge despite symptom relief , reflect the failure of treatment and is considered one of the strongest predictors of mortality [87]. This highlights a lack of correlation between weight loss and decongestion [4,9].

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The main goal for patients admitted with acute decompensated heart failure is to prevent residual congestion. To do so, one must thoroughly assess the patient at admission for possible features that might lead to residual congestion. For example, it is important to distinguish from the beginning what is the mechanism responsible for congestion: 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 guide dose escalation of loop diuretics or bail-out therapy through ultrafiltration [5,9,82,88]. Chronic use of loop diuretics in patients with chronic heart failure might lead to diuretic resistance, impeding decongestion in case of a decompensation episode [89]. This phenomenon is explained by hypertrophy of the distal tubular renal cells through compensatory sodium reabsorption, thus a reduction in natriuresis [90].

One efficient way to tackle residual congestion, according to the position statement of the Heart Failure Association of the ESC (HFA ESC) [5] , 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 [5]. Of course, this is done until the maximal dose is achieved if natriuresis and urinary output are inadequate. But one should keep in mind the fact that loop diuretics need to be protein bonded and dosed according to protein plasma levels for adequate secretion in the proximal tubule. Low levels of plasma proteins due to chronic loss or low production hampers plasma refill from the interstitium and thus delivery of loop diuretics to the kidney [91]. 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 congestion, especially in patients with advanced heart failure is hypochloremia. Hypochloremia is not only a marker of bad prognosis, it also promotes sodium retention and is associated with diuretic resistance [92]. This was first noted in the 1950's by Rubin Albert *et al*, where patients treated with mercurial diuretics developed hypochloremia and diuretic resistance which was eventually counteracted with the administration of exogenous lysine chloride with restoration of the diuretic response [93]. Low chloride levels stimulate renin secretion and the up-regulation of NaCl channels in the distal tubule thus leading to the increase of sodium reabsorption [94]. These mechanism insights led to the concept of administering hypertonic saline in conjunction with loop diuretics to augment diuresis [95,96]. Theoretically, lone hypertonic saline can restore low chloride levels and prevent sodium retention, osmotically shift fluid into the intravascular compartment, as well as temporarily reduce neurohormonal activation and thus improve diuresis [97]. However, a potential issue arises due to tubuloglomerular feedback, which could eventually result in a decrease in renal blood flow [97]. This can be overcome with the concomitant administration of furosemide, thuspotentiating diuresis. This was tested in several studies, where hypertonic saline was administered in conjunction with high-dose intravenous furosemide in comparison to standard therapy in patients with acute decompensated heart failure [95,96]. The results were: a higher effective diuresis, shorter hospital stay, improvement in symptoms and a reduction in hospital readmission [95,96]. Further randomized controlled studies are needed to clarify and validate this therapeutic regimen however it might be an option in those patients who have failed conventional therapies and are hyponatremic.

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 congestion. 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

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population is to improve venous capacitance and reduce cardiac filling pressures [57]. This can be achieved by adding vasodilators to low doses of diuretics as it can reduce preload and induce arterial vasodilation [98]. This is easier said than done because sometimes decongestion is not achievable due to hypotension, severe systolic dysfunction or severe pulmonary hypertension. That is why, there may be a need for inotropic usage or lowering heart rate. Numerous pharmacological agents are being tested to improve pulmonary capillary wedge pressure or venous capacitance but so far besides symptomatology, they failed to improve outcomes [98]. If the patient is hemodynamically stable, early introduction of neurohormonal blockers such as ARNi, iSGLT, MRA, and beta-blockers might reduce cardiac filling pressures, improve venous capacitance and fluid redistribution [57]. This strategy has been tested in STRONG-HF trial where an intensive treatment strategy of rapid up-titration of guideline-directed medication (at least two neurohormonal blockers) in stable hospitalized patients can overcome residual congestion and improve outcomes [100].

Diuretic resistance due to distal tubule sodium avidity can be overcomed by the use of thiazide or thiazide-like diuretics. These agents block the sodium-chloride cotransporter from the distal tubule promoting natriuresis and kaliuresis [101,102]. They enhance diuresis when used in combination with loop diuretics. However there are some major pitfalls when using these agents: their incapacity to dilute urine, they require protein binding to be secreted in the tubules, and they are independent predictors of hyponatremia and hypokalemia with an increase in all-cause mortality [102,103]. 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 in comparison to the lowest dose in reducing NT-proBNP and increasing urinary output in patients with decompensated heart failure [104,105].

A tempting new otherwise old agent used to facilitate congestion in decompensated heart failure patients is acetazolamide. It is a carbonic anhydrase inhibitor that promotes sodium reabsorption in the proximal tubule, formally known for treating altitude pulmonary edema and glaucoma [4,5]. Because 65% of sodium is absorbed in the proximal tubule, inhibiting its absorption at this level through the carbonic anhydrase inhibitor will determine the increase in natriuresis and greater delivery of chloride to the macula densa with consequent reduction in neurohormonal activity [28]. It is only logical to use this agent to enhance diuresis and decongestion in order to achieve euvolemia. Acetazolamide was tested in ADVOR study by Mullens et al in 519 patients with acute decompensated heart failure which shows that the addition of acetazolamide to loop diuretics in patients with acute decompensated heart failure resulted in a more efficient decongestion with the same impact and side effects as in those from the placebo group [106]. However, there are some drawbacks to this strategy. Achieving a more efficient decongestion by adding intravascular (IV) acetazolamide to IV furosemide did not result in a reduction of all-cause mortality or rehospitalization for heart failure, which was the same between groups (29% vs 27%) [106,107]. Although a greater increase of natriuresis and urinary output was seen in patients with GFR < 40 ml/min/m2 from the acetazolamide group, this was counterbalanced by a greater extent of worsening renal function but it remains to be demonstrated whether this was primarily a positive sign of clinical decongestion or as a primary sign of acute kidney injury [106,107]. All in all, “better sooner than late” does not seem to apply when it comes to the prognosis of heart failure with this drug and further studies are needed.

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 [108,109]. There were numerous proposed mechanisms 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 congestion [110]. The biggest trial to test SGLT2 inhibitors in acute heart failure was the EMPULSE trial where patients were assigned to receive empaglifozin 10 mg daily or placebo [111]. The trial concluded that initiation of empagliflozin in patients with acute heart failure is safe, and well-tolerated regardless of

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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 [111]. However, the treatment was randomized at a median time of three days from hospitalization when patients were considered stable [111]. 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. Overall, the study failed to show a statistical improvement in diuretic response at 5 days and at discharge for dapagliflozin in comparison 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 [113]. The study has shown that empaglifozin-treated patients in comparison to those with standard treatment, experienced a 25% increase in 5-day urine output without kidney injury and with a greater decline in natriuretic peptide levels [113].

In summary, the usage of SGLT2 inhibitors in acute heart failure is not well established, especially as a means to overcome congestion and one should take into consideration the potential risks that might appear such as ketoacidosis or acute kidney injury in the "acute vulnerable phase" due to high lactate or inflammatory levels, hemodynamic instability or low blood pressure [114,115]. It is also safe to say that early initiation of SGLT2 inhibitors during heart failure admission is beneficial regarding short-term outcomes and tackling residual congestion.

7. Conclusions

It is crucial to understand the pathophysiology and clinical manifestation of the congestion phenomenon for better management of heart failure patients. By integrating simple tools such as pulmonary echography, cardiac filling pressure echocardiographic parameters or circulating serum congestion biomarkers, clinicians might predict a future congestion decompensation episode or even residual congestion after an acute episode of heart failure. This multiparametric approach for assessing congestion, might be especially useful for monitoring and guiding decongestive therapies.

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