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Congestion occurrence and evaluation in acute heart failure scenario: time to reconsider different pathways of volume overload

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Abstract
Although congestion is considered to be the main reason for hospital admission in patients with acute heart failure, a simplistic view considering idro saline retention and total body volume accumulation did not provide convincing data. Clinical congestion occurrence is often the tip of the iceberg of several different mechanisms ranging from increased filling pressure to extravascular fluid accumulation and blood flow redistribution. Therefore, the clinical evaluation is often restricted to a simple physical examination including few and inaccurate signs and symptoms. This superficial approach has led to contradictory data and patients have not been evaluated according to a more realistic clinical scenario. The integration with new diagnostic ultrasonographic and laboratory tools would substantially improve these weaknesses. Indeed, congestion could be assessed by following the most recognized HF subtypes including primitive cardiac defect, presence of right ventricular dysfunction, and organ perfusion. Moreover, there is a tremendous gap regarding the interchangeable concept of fluid retention and redistribution used with a univocal meaning. Overall, congestion assessment should be revised, considering it as either central, peripheral, or both. In this review, we aim to provide different evidence regarding the concept of congestion starting from the most recognized pathophysiological mechanisms of AHF decompensation. We highlight the fact that a better knowledge of congestion is a challenge for future investigation and it could lead to significant advances in HF treatment.

Keywords Congestion · Acute heart failure · Echocardiography · Laboratory biomarkers

Introduction

Congestion is the main reason for hospital admission in patients with acute heart failure (AHF). Around 90% of patients admitted for an episode of HF experience some signs of congestion. Volume overload and fluid accumulation are considered hallmarks of acute HF. The two main characteristics of congestion are sudden redistribution of blood volume from systemic to pulmonary districts and intravascular fluid retention. Unfortunately, a simplistic view taking into account idro saline retention, total body volume accumulation, and euvolemia restoration by common diuretic treatment did not provide enough convincing data or potential solutions. Currently, a universally recognized diagnostic algorithm which can grade congestion is lacking [1–3]. In different studies, diverse clinical and diagnostic tools have been used and the methods employed for its evaluation are generally too broad. Current discrepancies could lead to a different prognostic impact and management of residual congestion, although most trials agree in recognizing its prognostic value. Congestion is traditionally defined as an increase of LV diastolic filling pressure associated with typical signs and symptoms of HF [4, 5]. Clinical congestion appearance is the tip of the iceberg of cardiac dysfunction leading to increased filling pressure backward transmitted to the pulmonary circulation and central venous system. For this reason, its recognition by simple clinical examination is often delayed and the use of some new diagnostic tools appears mandatory for an early identification. Therefore, it could be classified in central and peripheral in relation to the involved organ damage [5, 6]. The interchangeable concept of volume overload and congestion should be addressed and specific monitoring which accounts for the intravascular or extra-vascular compartment and the main site of fluid retention are worth considering. These simple assumptions suggest that the congestion cascade should be re-examined in a more integrated model that recognizes

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systemic and cardiac congestion as two distinct processes. Moreover, the congestion occurrence may be analyzed looking at different HF subtypes, the clinical presentation and the temporal trend (i.e., worsening HF vs de novo HF).

The prognostic role of congestion

Although congestion is related to poor outcome, its precise clinical assessment is often misleading, and in the case of evaluation, this is not performed with a systematic method because a validated score at admission and before discharge is still not endorsed. Despite the different methods employed, many trials confirmed the prognostic role of congestion. Indeed, it is one of the principal goals during treatment of the acute phase: in the ACTIVE HF trial, when evaluating the prognostic impact of vasopressin-2 antagonist, patients who experience increased jugular venous pressure, dyspnea at rest, and edema have a 3-fold increased risk of hospital readmission and death during a short time follow-up period [7]. In the more recent PROTECT trial, by evaluating adenosine-2 receptor antagonist Rolofilline, the authors graded dyspnea and those subjects with early dyspnea relief and greater weight loss showed a reduced mortality with respect to patients with persistent dyspnea after 3 days of treatment [8]. A more detailed post hoc analysis from the EVEREST trial evaluated congestion by clinical assessment and severity signs. The authors divided congestion among quartiles and patients with higher scores had a poor prognosis. A current study revealed that around 40% of patients were discharged with some signs of residual congestion [9]. The EURO survey program confirmed such a trend, showing that during acute phases, only 24% of patients had a complete congestion resolution, and their mean weight loss was at least 2 kg [10]. This feature is not surprising when assuming that residual congestion is inversely related to the length of hospital stay and most likely to be caused by incomplete treatment and drug titration. These current findings have been recently replaced in patients with either reduced systolic function (HFrEF) and preserved systolic function (HFpEF) over a 3-month follow-up period [11]. Finally, a post hoc analysis by the CARESS and DOSE trials, respectively, conducted in patients submitted to ultrafiltration and furosemide treatments, residual congestion was related to poor outcome at 90 days [12]. Despite this data, congestion remains difficult to assess, especially when symptoms are mild and patients are prone to recurrent episodes. Therefore, an evaluation by means of clinical signs is superficial and it could hide effective cardiac filling pressure increase. For these reasons, numerous scores based on clinical evaluation, imaging tools, and biological tests are available to assist physicians in ascertaining and quantifying congestion [13–15]. Overall, congestion recognition at an early stage by an integrated clinical laboratory and ultrasonographic assessment remains one of the principal goals for future research [16].

Congestion modality assessment

Over recent years, several authors proposed a few models including echocardiographic parameters, lung ultrasound, chest x-ray, and additional clinical assessment, to optimize and grade congestion [14–16]. Despite advances in diagnostic tools, clinical examination still appears to be fundamental for an acute HF classification and initial management. Although the clinical approach has some weaknesses, it remains central for HF categorization following the Stevenson criteria. During a clinical visit, it is possible to establish patients' volume status and peripheral perfusion [17]. However, a standardized protocol indicating the parameters to be included and the evaluation timing course is still lacking. Recently, a position paper by the ESC HF group suggested the use of a flow chart including either clinical, echocardiographic, and lung ultrasound measurements to detect congestion more precisely [18]. Most studies are restricted to the clinical evaluation: when assessed, the traditionally recognized signs are dyspnea, ortopnea jugular vein distension, epatojugular reflex hepatomegaly, peripheral edema, and third heart sound; chest radiography, although included in the initial diagnosis and evaluation of AHF, is considered in only a few studies. The traditional evidence of cardiomegaly, venous hypertension, and fluid lung redistribution until the interstitial edema is not believed to be specific targets [19, 20]. The ADHERE registry confirmed approximately one of every five patients admitted from the Emergency Department with acute decompensated heart failure had no signs of congestion on chest radiography [21]. This indicates that physicians should not rule out subjects with negative radiographic signs and a careful clinical examination needs to be undertaken on patients presenting with dyspnea. Alternative signs of congestion are pulmonary rales, body weight changes, Valsalva manoeuvre and dyspnea on exertion. All these markers include some weaknesses due to scarce specificity and inter-observer variation leading to a modest accuracy.

Although the above cited signs are acknowledged as universal parameters for congestion detection, other protocols take into consideration different factors: in the PROTECT trial, the heart rate, blood pressure, respiratory rate, natriuretic peptides, and the NYHA class were considered as the primary end point for good a good response to treatment [8]. In the ESCAPE trial, besides the pulmonary catheterization measurement, the included congestion signs were only dyspnea, edema, jugular venous pressure, and body weight [22]. Conversely, in the post hoc analysis from the ASCEND-HF trial, the authors indicated body weight gain, blood urea nitrogen (BUN) increase, and low BNP level reduction as the congestion measurements most related to an adverse outcome [23]. More recently, Harjola et al. from the ESC-AHF committee suggested a score based on organ injury due to congestion. In this document, the authors intend to provide a better

identification of target organ damage by an assessment of heart, kidney, lung, abdomen, and brain [24]. However, the evaluation of organ deterioration is not only limited to a physical examination as it also includes laboratory markers, echocardiography, lung and abdominal ultrasound. In line with these assumptions, and with the concept of organ crosstalk between different organs, mediated via mechanical, soluble, and cellular mechanisms, a cardio-pulmonary renal syndrome has recently been described [25]. This crosstalk could be reordered by congestion, starting from increased cardiac filling pressure towards pulmonary venous congestion, increased right atrial and central vein pressure, up to renal vein elevation and kidney congestion. The wide range of the adopted criteria leads to a dishomogeneous evaluation during the physical examination, and an unmet need of criteria standardization appears mandatory, both in terms of parameters and in terms of the timing course evaluation. Both aspects could potentially create an enormous bias and they must be clarified. Therefore, specific guidelines should be devised to standardize this topic. As suggested by the recent position paper, the simple application of a clinical congestion score based only on symptoms and signs has limited value and it should be integrated by new diagnostic features [18]. These would probably include ultrasonographic parameters associated with available laboratory markers including natriuretic peptide, osmolarity, and hemoconcentration. Despite all these theories, congestion classification and assessment in HF (by universally recognized and easily detectable criteria) remain an unmet need and a goal for future studies.

Different congestion scenario in heart failure subtypes

Acute HF presentation encompasses a wide spectrum in relation to the prevalent underlying pathophysiological mechanisms, organ perfusion, and congestion. Acute HF can occur as hypertensive HF, pulmonary edema, right HF, HF associated with acute coronary syndrome (ACS), and cardiogenic shock. Besides, on the basis of temporal criteria, acute HF could be divided into de novo heart failure or worsening decompensated chronic HF [26]. Data from the ESC registry showed that most patients (61%) presented with acute decompensated HF, 13% had pulmonary edema, 14% experienced ACS, and only 3% had cardiogenic shock, confirming the heterogenous picture of acute HF syndrome [27]. The OPTIME HF demonstrated that most episodes are related to congestion and only 10% to hypoperfusional defect. Moreover, 42% experienced some precipitating factors causing clinical deterioration status, and among the initial causes, around half can be attributed to extracardiac reasons [28]. Another classification, beyond the timing course, focused attention on the presence or absence of CAD and the main cardiac defect in terms of preserved or reduced ejection fraction. Accordingly, data from the ADHERE registry showed that patients with HFpEF were more likely female, had a history of hypertension, less coronary artery disease, and a lower risk of inpatient death but a higher likelihood of deterioration in renal function during hospitalization [29]. All these phenotypes could appear in completely different modalities: this depends on congestion severity and variety of congested systemic organs. Therefore, the primitive cardiac dysfunction, left or right congestion, and normal or low cardiac output play an important role in congestion status. Overall, a greater pathophysiological understanding of the different congestion features of the various AHFS is needed in order to identify targets for therapy and research. This includes not only idro saline retention but also hemodynamics, neurohormonal overdrive, inflammatory activation, and the cardiorenal crosstalk.

Looking at the post hoc analyses of DOSE and CARESS, no significant differences in terms of the dyspnea score, ortopnea, peripheral edema between HFpEF and HFrEF were demonstrated [30]. Therefore, any significant discrepancies regarding echo findings and laboratory parameters between the two groups have been revealed [31]. However, both studies did not measure congestion following the more recent suggested criteria and the evaluation was restricted to the dyspnea score, Jugular venous pressure, pheripheral edema, and NP measurement. Only the Van Aelst partially analyzed echocardiographic parameters regarding pulmonary pressure and cava vein.

Conversely, congestion appearance is different in isolated right HF with respect to left HF. In the former, congestion is mainly due to increased central venous pressure leading to epathomegaly gut congestion and pheripheral edema. In the latter, congestion is the consequence of increased filling pressure with pulmonary hypertension and lung congestion. The current picture could vary in relation to the timing of increased pulmonary pressure, presence of contemporary right ventricular dysfunction, and systemic conditions in terms of stroke volume and mean arterial pressure [32].

Similar divergencies regarding lung involvement in terms of extravascular water accumulation and pleural effusion may be found in either HFpEF and HFrEF [15, 33]. Current odds have been updated in a cluster analysis identifying three main phenotypes with different clinical characteristics: cluster 1 had the highest average systolic blood pressure at admission and lung congestion. Cluster 2 represented subjects with both "cardiac and renal failure" low EF and poor renal function. Cluster 3 comprised mostly older patients with the high prevalence of atrial fibrillation and preserved EF [34]. In line with these theories, when a panel of 37 different biomarkers were analyzed in the PROTECT trial, the authors revealed that subjects with HFrEF had an increased value of biomarkers related to cardiac stretch and volume overload whereas in HFpEF,

biomarker interactions were mostly related to inflammatory activation and fibrosis [35]. Accordingly, the BIOSTAT network analysis showed that biomarker profiles specific for HFrEF are related to cellular proliferation and metabolism, whereas biomarker profiles specific for HFpEF are related to inflammation and extracellular matrix reorganization [36]. The current differences reflect the end of life and death modalities in both subtypes: in HFrEF, the main causes of death are low output state, end stage worsening congestion status, and sudden death due to ventricular tachiarrythmia; in HFpEF, a consistent percentage of deaths are related to non-cardiovascular reasons, to systemic vascular accidents, and to right heart failure [37] (Fig. 1).

Many other factors distinguish systolic and diastolic HF: HFpEF is associated with impaired LV diastolic function and significant ventricular and aortic stiffening. The degree of aortic stiffness and reduced arterial compliance suggests central and peripheral vascular derangements as two main factors in HFNEF-pulse wave velocity measured in the arterial arm, which was significantly higher in HF-PSF subjects than in both HF-RSF. Conversely, venous capacitance was higher in HFrEF subjects compared with HFPEF subjects [38]. The Swedish heart failure registry has recently confirmed a close association between PP and HF that increases linearly with EF [39]. Current divergences could be emphasized during exercise stress in around 50% of HFpEF patients developing pulmonary hypertension. Reduction in arterial elastance and ventricular-arterial interaction was attenuated owing to a minor elastance increase in HFpEF [40].

Qualitative studies have also documented that patients with HFrEF develop more severe symptoms than those with HFpEF and are associated with more significant exercise intolerance, frequent hospitalizations, right heart failure, and reduced survival. The current clinical scenario may be partially explained by baseline and demographic characteristics in the two subtypes: patients with systolic dysfunction are more frequently younger males with prevalent CAD and normal or low blood pressure value, mostly with a history of recurrent episodes, whereas subjects with diastolic dysfunction are more frequently older females with several associated metabolic disorders, with higher blood pressure values with respect to the previous group. All these items could explain the different manifestations of congestion volume overload that appear predominant in patients with acute HFrEF where weight gain associated with a significant degree of systemic venous congestion is typical. Otherwise, patients presenting with normal or elevated blood pressure (HFpEF) exhibit much more pulmonary congestion rather than systemic congestion and little weight increase [41]. Further differences are related to pulmonary hypertension occurrence and pulmonary vascular remodeling [42]: in a retrospective study, Guazzi et al. found that despite similar levels of wedge pressure in HFpEF and HFrEF, pulmonary circulation is stiffer in patients with HFpEF-PH than in patients with HFrEF, leading to a higher diastolic pulmonary gradient [43]. The same group previously demonstrated a different echocardiographic pattern significance of right ventricular (RV) dysfunction that correlates with the prognosis in patients with reduced (HFrEF), mid-range (HFmrEF), or preserved (HFpEF) left ventricular ejection fraction [44]. Although a specific association between the pathophysiological mechanisms of congestion and left ventricular ejection fraction is obtained only through clinical signs, no studies have demonstrated specific hemodynamic and neurohormonal models in different subtypes [45]. Based on these assumptions and evidence, the Cotter theory, indicating cardiac and vascular congestion, needs to be updated: acute decompensated HF resulting from decreased myocardial contractility and impairment of previous deteriorated cardiac performance leading to fluid retention; the second form is characterized by rapid increase of systemic pressure and systemic vascular resistance, altered ventriculo-arterial coupling with afterload mismatch and superimposed left diastolic dysfunction [46]. Thus, the primitive cardiac defect instead of simple fluid accumulation may play a fundamental role and it could create a different congestion scenario.

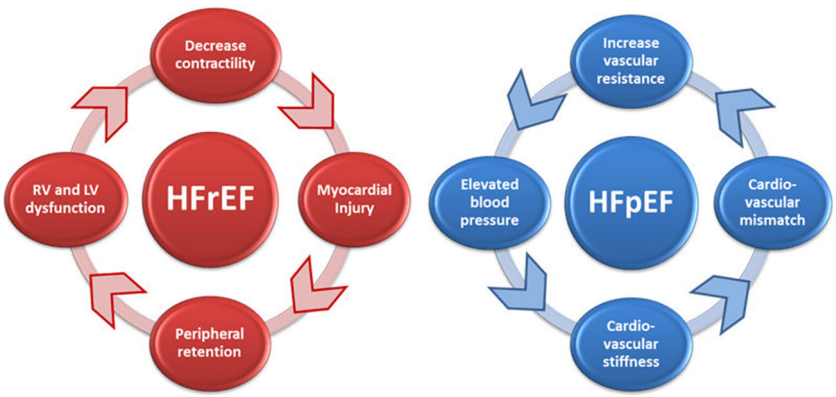

Fig. 1 Different pathophysiological mechanisms of in congestion and death in HFpEF and HFrHF

Central and peripheral congestion: two sides of the same coin?

The existing paradigm for understanding congestion in acute HF focused primarily on volume overload and left ventricular filling pressure elevation. The traditional model regards cardiac dysfunction with inadequate cardiac output for metabolic and systemic organ function as the main factor. This primitive failure leads to peripheral vasoconstriction and initial increase of venous return mediated by neurohormonal activation to maintain adequate organ perfusion. The initial beneficial effects of these mechanisms become harmful over a long time period; the idro saline retention and fluid volume overload with consequent blood volume expansion are the main drivers of more advanced stages [47]. The mismatch occurring among cardiac contractility, increased stiffness, augmented afterload, and reduced preload causes a further increase in left ventricular filling pressure with both forward and backward HF. The latter dysfunction creates a left atrial pressure increase, reduced pulmonary vein return, and capacitance associated with post capillary hypertension. Pulmonary congestion is the final situation that occurs due to blood flowing upstream into the left cardiac chambers and to increased pressure in pulmonary capillaries that are not compensated by lymphatic drainage [48, 49]. The increase of the fluid filtration rate from the interstitium and altered drainage capacity shifts fluids from vascular to the interstitial bed. Capillary pulmonary permeability, vascular endothelial properties, and pulmonary arterial vessel thickening could develop a contemporary pre capillary hypertension [50]. All together, these factors contribute to an increased mean and systolic pulmonary pressure elevation, wedge pressure increase with eventual right ventricle remodeling and dysfunction. Maladaptive RV remodeling appears to be a consequence of continuous RV pressure overload, leading to tricuspid regurgitation and subsequent systo-diastolic dysfunction [51, 52]. These mechanisms also lead to RV dissynchrony, which depends on RV myocytes that prolong their contraction time delaying the systolic leftward septal movement. Another causal factor of maladaptive remodeling is ventriculo-arterial uncoupling, which represents the lack of relationship between RV contractility and afterload [53, 54]. Persistent RV deterioration can cause increased central venous pressure, reduced venous return, and pre-load condition, with peripheral edema and jugular venous distension occurrence.

On the other side, increased RAA and sympathetic activities enhance water and sodium reabsorption into the kidney, to maintain adequate filtraction fraction. Unfortunately, the persistent neuro endocrine activity induces detrimental effects on both the heart and kidney. In the cardiovascular system, LV hypertrophy and remodeling are developed; it accelerates fibrosis and apoptosis processes and peripheral vasoconstriction occurs in order to increase plasma volume. At kidney level, it provides intrarenal blood flow redistribution, reduced medullary blood flow, glomerulosclerosis, tubular fibrosis, and efferent and afferent arterial vasoconstriction [55]. Sympathetic stimulation causes peritubular capillary oncotic pressure elevation and it reduces peritubular capillary hydrostatic pressure with a consequent increase in sodium resorbtion in the proximal tubule. Angiotensin II also stimulates sodium resorption via two mechanisms: a direct effect at medullary level stimulating the synthesis of renin by the macula densa and indirectly by the aldosterone production, which in turn activates Na K exchange in the distal collector duct. These features result in interstitial fluid accumulation with a reduction in effective circulating blood volume [56, 57].

Because around 40% of blood volume physiologically resides in the arterial district and this percentage is reduced during HF, a substantial volume expansion is necessary to preserve organ perfusion. This is obtained by an altered blood volume and interstitial volume expansion that become the main drivers of clinical and organ congestion. Another actor to be accounted in this framework is the venous district: it contains approximately 70% of total blood volume and it is much more compliant than the arterial system. Therefore, a relevant numbers of α_1 and α_2 adrenergic receptors are lodged in splanchnic veins, making them highly sensitive to adrenergic stimulation [58]. These anatomic findings imply that for a given sympathetic stimulus, the veins respond to a much greater degree than the arteries. The final result is that sympathetic activation reduces venous capacitance increasing both central and peripheral vein pressure. Current mechanism leads to a reduced venous return accelerating capillary permeability and interstitial fluid accumulation. Taken together, all these mechanisms cause a fluid shift from the venous vessels to the extravascular volume expansion, culminating in the syndrome of congestion (Fig. 2) [59].

These assumptions mean that two distinct mechanisms contribute separately and mutually to the congestion and we can clearly distinguish a central congestion from a peripheral congestion. This current concept was confirmed by the ESCAPE data revealing that worsening renal function was not related to cardiac output, pulmonary wedge pressure, and systemic vascular resistance. Conversely, there was a weak correlation with right atrial pressure [60]. Current findings suggest that in patients with invasive monitorization, the relationship between heart failure and renal dysfunction is more complex than hemodynamics alone. Therefore, they confirmed that some discordances exist between cardiac congestion and liquid retention [61]. Despite the fact that continuous monitorization in both HFrEF and HFpEF found a close relation between increased pulmonary pressure and events recurrence in intensive care ward patients, other data did not show any type of relationship existing between central venous pressure and total blood volume. Interestingly, by using albumin-labeled radioiodate injections, Miller et al. demonstrated a wide distribution of TBV plasma volume and red cell volume [62]. Therefore, after diuretic administration, any differences were

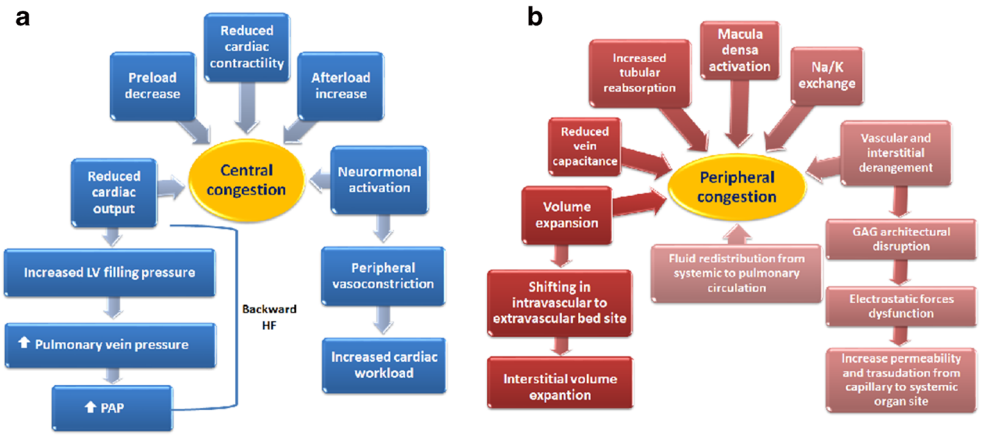

Fig. 2 Central (**a**) and pheripheral (**b**) congestion pathways supposed in acute HF

observed in terms of delta TBV and PV before and after treatment. Current data confirm the heterogeneity of body fluid accumulation and blood redistribution during HF condition.

The role of the third space: the intrestitium site

Despite the consideration of volume overload as a hallmark of acute HF, the pathophysiology of fluid accumulation and redistribution remains understood only in part. Similarly, although it is known that hemodynamic congestion precedes pulmonary and peripheral congestion, there is no concordance between body weight gain and invasive measurement. Such discordance could be partially explained by taking into account the extravascular bed: the balance occurring between intravascular and interstitial space is normally modulated by Starling forces across the capillary wall integrity that guarantees an equilibrium resulting in stable no net movement of fluid in steady-state conditions [63]. However, the decrease in capillary hydrostatic pressure as occurred in HF with impaired cardiac output results in a shift from interstitial fluid into the intravascular space in an attempt to restore effective circulating BV and maintain normal organ perfusion. This reserve capacity of the interstitial fluid compartment provides a compensatory mechanism to support PV expansion in patients with HF. Despite these recognized mechanisms, there is a wide heterogeneity because of multiple confounding factors that influence a uniform answer: differences in systemic systolic blood pressure, opposing oncotic forces, changes in capillary permeability, lymphatic drainage, the degree of neurohormonal activation, renal function, and tubular Na resorption are highly variable and, therefore, make the extent of BV expansion highly variable [63, 64].

Secondly, 30–35% of total BV is in the arterial district 50% in the vein bed and the resting 15% in the interstitium. At capillary level, a shift in the distribution of body fluid between the interstitial and the intravascular fluid compartments could occur. This is caused by transcapillary oncotic increase and hydrostatic pressure reduction promoting transudation in the interstitium whereas low interstitial compliance opposes fluid accumulation [65]. Thirdly, the extent of interstitial volume expansion and, therefore, BV expansion depends on the severity of HF, which in turn is related to neurohormonal activation, vasopressin activity, and renal sodium avidity [66]. In this picture, interstitial glycosaminoglycan integrity plays a considerable role in the permeability regulation. Recent insights suggest that Na^+ is not distributed in the body solely as a free cation, but that it is also bound to large interstitial glycosaminoglycan (GAG) networks in different tissues. The GAG structure consists of elastin fibers and collagen, in which the equilibrium is maintained by electrostatic forces depending on the Na concentration. For each increase of Na, from both dietary intake as well as retention depending on tubular reabsorption, we have structural damage and architectural destabilization linked to a sudden increase of Na. This increase alters the electrostatic equilibrium with a rise in interstitial oncotic pressure, a reduction in hydrostatic pressure, and further shifting of liquid from the intravascular to the extravascular bed [64]. Therefore, endothelial glycocalyx (eGC) consists of a network of different types of soluble proteoglycans and glycoproteins that are connected to the endothelial cell membrane through adhesion molecules. A dynamic equilibrium exists between the eGC and flowing blood, which continuously affects its composition and electrostatic gradient. In normal conditions, it reduces vascular permeability, restricts molecules from reaching the endothelium, and avoids platelet adhesion. Most importantly, the endothelial GAG network acts as a Na^+ buffer by binding positively charged Na^+ cations. As a result, the eGC buffer allows the gradual passage of Na^+ from the blood into the space between the eGC and endothelium [67]. Na^+ can subsequently enter the endothelial cell through apical endothelial Na^+ channels. Then, sodium-potassium adenosine triphosphatease restores cell homeostasis by creating a transcellular passage for Na^+ into the interstitium. However, most Na^+ is transported between endothelial cells along its

electrochemical gradient via the paracellular pathway. Any damage occurring at the endothelial glycocalyx (eGC) leads to increased vascular permeability, diminished sodium (Na^+) buffer capacity, and disturbed mechanotransduction [68].

Based on these hallmarks, the congestion cascade could be re-examined in a more systematic model, looking at the integrity and composition of the interstitium. Overall, the intra and extravascular congestion by specific diagnostic tools measuring the entity and variety of fluid accumulation is worth investigating.

New application for grading congestion

Because the diagnostic accuracy of congestion based on clinical signs, dyspnea score, and chest radiography is quite inaccurate, a non-invasive algorithm has been recently updated and it accounted echocardiography, chest echography, and laboratory tools [5, 18]. This statement proposed a series of applicable measurements easily detectable in clinical practice.

Echocardiography Comprehensive echo examination provides useful information about cardiac structure and function: by cardiac ultrasound examination, it is possible to establish the whole systolic function, kinetic abnormalities, presence of valve disease, and myocardial mass. Thus, echocardiography appears mandatory during the early evaluation phases, because of its accuracy in recognizing the main patho-physiological mechanisms of AHF: the most traditional parameter of systolic function detection is ejection fraction by which we categorize the type of HF in reduced (EF < 40%), preserved (EF > 50%), or mid-range HF (EF between 40 and 50%) [69]. This achievement is relevant to identify the primitive cardiac function defect and may be matched with blood pressure value in order to recognize systemic organ perfusion and cardio vascular coupling interaction. Another important item we can obtain by cardiac ultrasound is the RV condition and adaptation. Although reproducibility and correlation with true RV volumes invasively measured are often misleading, its assessment by echocardiography demonstrated a close relation with prognosis. Indeed, echo modality has got some intrinsic limitations related to acoustic window and the inability to completely detect the whole RV volume by traditional approach. Thus, formula applicable for systolic LV evaluation cannot be reproduced for RV: its different shape, contraction modality, free wall characteristics, and the lack of specific anatomic references points, make it difficult to extend calculations validated for LV [70]. RV systolic function can be also evaluated using multiple methods: tricuspid anular peak systolic excursion (TAPSE) is the simpler and more accurate parameter measuring lateral anulus movement in M-mode reflecting longitudinal RV function but even the effective systolic function. It is easily applicable with best reproducibility and it provides useful information of RV status among other echo parameters. Because of these, characteristic is recommended for evaluation and assessment in patients with primitive or secondary pulmonary hypertension. Systolic wave velocity (S′) obtained by TDI signal is the measure of free wall contraction at basal level obtained by the average of three cardiac cycles. It is prone to loading condition and heart rate as well as RV strain and strain rate calculated as percentage of RV free wall systolic shortening by speckle tracking modality. The analysis of LV filling pressure by transmitral flow and early diastolic tissue wave (E/e^1) ratio provides useful information and details on intracardiac LV pressure and overload. Another important feature available by Doppler ultrasound is pulmonary systolic pressure by the tricuspidal regurgitation using Bernoulli equation. Recently, the combination of TAPSE and PASP ratio has been proposed as a surrogate marker of RV-vascular coupling. This new variable showed a strong relationship with prognosis in chronic HF patients with both reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) [71, 72]. Finally, the right atrial pressure could be estimated by the collapsibility of inferior vena cava (VCI) during respiratory excursions. Despite several non-invasive diagnostic methods have been described to assess PH and RVD in chronic conditions, poor data are reported in acute setting during early hospitalization phase. Future researches may confirm whether these parameters will be related to outcome in acute setting and whether a decrease of VCI, PASP, and E/e^1 ratio after acute treatment will be really associated with effective adverse event reduction.

Lung echography Ultrasound lung comets (LUS) assessment is a simple, accurate, fast, and economic tool to assess pulmonary congestion and detect milder degrees of congestion that might benefit from an intensification of therapy. The number of B-lines is directly proportional to the severity of lung congestion. B-lines measured were also related to clinical evidence of pulmonary congestion, a raised plasma BNP, increased echocardiographic measures of left ventricular filling pressure, left atrial dilatation, raised pulmonary artery pressure, and inferior vena cava distension [15, 73]. Accordingly, B-lines appear useful, in addition to B-type natriuretic peptide (BNP) and chest X-ray, for the differential diagnosis of suspected AHF as suggested by current guidelines. [74] Residual pulmonary congestion evaluated by LUS before discharge identifies patients with greater unmet needs who might benefit from experimental interventions [75, 76]. Again, it must be emphasized that dyspnea disappearance should not be considered the same as resolution of pulmonary congestion. In this setting, LUS assessment seems to be superior with respect to chest radiography, with real-time, low-cost, and radiation-free advantages. Indeed, chest radiography could be negative in 20–30% of patients particularly those with chronic pulmonary vein hypertension [77]. More than three B-lines in each intercostal space are suggestive of interstitial edema.

Natriuretic peptides The most known laboratory markers employed in HF diagnosis are natriuretic peptides (NP).

Both BNP and its precursor NT-pro-BNP are related with LV end diastolic pressure and pulmonary pressure [78]. Therefore, in acute setting, significant BNP level increase is a reliable sign of severe diastolic dysfunction confirmed by the relationship with high E/e1 ratio and signs of pulmonary congestion [79, 80]. From the OPTIMIZE data, discharge BNP compared with other clinical variables was the most important factor for 1-year adverse event prediction [81]. A meta-analysis including 19 studies significant levels decrease of both BNP and NTproBNP from admission to discharge was associated with reduced risk of readmission and worsening HF [82]. Therefore, in a group of patients, candidates for heart transplantation, the BNP-guided management combined with peak exercise oxygen consumption test was indicative for cardio surgery and a cut off value less than 506 pg/ml showed an identical course with respect to survival transplanted patients [83]. Despite these findings, some concerns are recently raised about the natriuretic peptide (NP)-guided treatment and prognostic role of NP in HFpEF: indeed, in the TIME-CHF trials, NTproBNP-guided therapy did not improve HF hospitalization free survival [84]. Moreover, the GUIDE IT study conducted to optimize BNP level below 100 and NTproBNP below 1000 pg/mL in patients with different NYHA class, showed equivalent outcome in active arm vs standard treatment in terms of both adverse events and quality of life [85]. Beyond specific studies, some unresolved concerns deserve specific attention and NP measurement needs to be contextualized thinking of the following question: NP levels have got similar diagnostic and prognostic powerful across the whole spectrum of HF? Which is the best NP threshold for guiding management? What is the best timing for blood samples and optimal delta biomarker-guided HF care? Which is the significance of "non responders"? [86, 87] Finally, NP measurement should be evaluated accounting for sex, age, body mass, chronic kidney diseases, and inflammatory conditions.

Adrenomedullin Adrenomedullin (AM) is a new biomarker expressed in the adrenal glands, heart, lungs, and kidneys, vascular endothelium with vasodilatory action originally discovered in human pheochromocytoma tissue. AM receptors are distributed throughout the cardiovascular system and have been identified in the heart and lungs [88]. AM acts as an autocrine and/or paracrine peptide to play a key role in the regulation of water and sodium homeostasis [89]. Given to its vasoactive properties, AM levels are physiologically elevated during pregnancy and its precursor proADM is blunted in severe preeclampsia [90]. Both AM proAM are all higher in patients with heart failure than healthy subjects in proportional to the disease severity. The BACH study revealed that MR-proANP levels have additional diagnostic significance compared to BNP levels in patients with intermediate BNP levels. MR-proANP is as useful as BNP for AHF diagnosis in dyspneic patients and may provide additional clinical utility in subgroup with grey zone BNP value [91]. Despite these positive results, current biomarkers should be still tested in a randomized trial study and the precise mechanism of increase needs to be furtherly investigated.

Hemoconcentration Increased hemoglobin (HB) and hematoctitc (Hct) levels over treatment for HF are now accounted

Table 1 Clinical signs, instrumental and laboratory features for congestion detection: advantages and disadvantages for each method

Parameter	Strength	Weakness
Clinical evaluation		
JVP (mm)	High correlation with pulmonary pressure	Difficult in obese patient
Hepatomegaly	High correlation with right atrial pressure and systemic organ congestion	Poor sensitivity in patient with de novo HF
Peripheral edema	High sensitivity for hydrosaline retention	Poor correlation with cardiac output
S_3	Indicative of increased LV filling pressure and central congestion	Poor correlated with peripheral congestion
Rales	High accuracy in pulmonary edema	Poor sensitivity in patient with chronic precapillary hypertension
Echocardiographic evaluation		
IVC (mm)	Good correlation with right atrial pressure	Poorly indicative of LV performance and cardiac output
Lateral E/e′ > 12	Indicative of high LV filling pressure and severe diastolic dysfunction	Not easily valuable in acute setting and in patient with tachyarrhythmia
sPAP evaluation (mmHg)	Highly sensitive and related to wedge pressure	Poor sensitivity in patient with poor acoustic window and in patient with low ventricular/atrial gradient
TAPSE (mm)	Related to function of RV	Not easily detectable by ecofast and in patient with poor acoustic window
Diffuse B-lines on lung ultrasound	Better than chest x-ray in the evaluation of pulmonary congestion	Poor accuracy in patient with pneumonia
Laboratory		
BNP and NT pro-BNP	Useful for diagnosis of HF and for guiding therapeutic decisions	High levels in AF, elderly and renal failure. Low levels in obese patient and HFpEF
Hemoconcentration	Signal of adequate decongestion in HF treatment, useful for volume assessment	Relative information about total blood volume and extravascular congestion
Adrenomedullin	Correlated with interstitial lung retention and pleural effusion	Poor information about cut off prognostic value

AF atrial fibrillation, *BNP* B-type natriuretic peptide, *HF* heart failure, *IVC* inferior vena cava, *JVP* jugular venous pulsation, *RV* right ventricle, *sPAP* systolic pulmonary artery pressure, *TAPSE* tricuspid anular plane systolic excursion

as indirect markers of decongestion. Several studies described a relation existing between hemoconcentration and favorable outcome: in a post hoc analysis from the EVEREST trial Hct increase from admission to discharge was associated with less congestion and decreased mortality despite renal impairment occurrence during hospitalization [92]. Similarly, a single center study showed around 38% of patients experienced any type of concentration and this trend occurred in both HFrEF and HFpEF. Therefore, distinguishing between transient or persistent hemoconcnetration, only the latter was related to improved outcome [93]. Aggressive diuretic therapy and good diuretic response are markers for better fluid removal, clinical decongestion leading to hemoconcentration. Additionally, WRF occurrence in the setting of hemoconcentration is not related with adverse events and it may simply identify those groups with increased fluid depletion or higher vulnerability to rapid fluid changes [94]. (Table 1).

Tumor marker antigen carbohydrate 125 Tumor marker antigen carbohydrate 125 (CA-125) levels have shown a correlation with the severity of fluid overload and the risk of mortality and readmission. CA-125 is a glycoprotein widely used for ovarian cancer and abdominal diffusion monitoring, and it has emerged as a potential biomarker of heart failure (HF). Plasma CA-125 correlates with clinical and echocardiographic parameters related to increased central venous pressure, abdominal, and pleural effusion and liver congestion [95, 96]. Particularly interesting is the correlation with symptoms and signs of right HF and inflammatory markers. Indeed, high levels of this glycoprotein have shown to be present in most patients admitted for AHF and independently related to mortality and subsequent admission for AHF [97]. Therefore, CA-125 levels appear reduced during a aggressive decongestive therapy, for this reason could be of potential interest to monitor the reduction of liquid in the sierose membranes during acute treatment [98].

Plasma osmolality Plasma osmolality is an indirect marker of intravascular liquid overload and it is directly related to sodium, blood urea nitrogen (BUN), and glucose. It has been suggested that low discharge serum osmolality was independently predictive of postdischarge mortality and readmission [99]. In the EVEREST trial, plasma osmolality was reduced in the active arm, whereas in the placebo group, it tends to increase throughout hospitalization. However, this effect on osmolality declined in the early post-discharge period; its reduction was associated with improvement of congestion signs [100] Whether vasopressin (AVP) release in response to both osmotic and nonosmotic stimuli and its consequences on water fluctuation has a clinical impact in HF must be investigated by cross-sectional researches.

All together, these biomarkers assay associated with careful clinical and echo examination could provide a better idea of extravascular and intravascular fluid retention, organ congestion much more involved and hemodynamic status. This method could help physicians in the decision making and better individualized strategy in relation to the congestion scenario.

Conclusions

Congestion is the main feature of acute decompensated HF and it is often anticipated by several signs behind the traditional dyspnea. By a combined clinical laboratory and imaging examinations, we are now able to identify cardiac and systemic congestion through an integrated analysis [101, 102]. Unfortunately, by now, a wide range of criteria conduced to a lack of uniformity in the decision making. Thus, an unmet need of criteria standardization appears mandatory both in terms of adopted parameters as in terms of timing course evaluation. Indeed, persistence of subclinical congestion quantified by combined ultrasound and NP assessment might help in guiding treatment, facilitate personalized therapy, and avoid future events. In conclusion, it could be time to take a step back and give much more importance to the congestion typology and fluid accumulation occurrence that could differ in the different HF scenario. A universal acknowledgement of clinical and cardiac congestion, vascular redistribution, and intravascular fluid overload appears mandatory to better stratify our patients. Current topics will become an increasingly significant area of interest and a challenge for future research.

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