Congestion in heart failure: a contemporary look at physiology, diagnosis and treatment

Eva M. Boorsma[1], Jozine M. ter Maaten[1], Kevin Damman[1], Wilfried Dinh[2,3], Finn Gustafsson[4], Steven Goldsmith[5,6], Daniel Burkhoff[7,8], Faiez Zannad[9], James E. Udelson[7] and Adriaan A. Voors[1] ✉

Abstract | Congestion is the main reason for hospitalization in patients with acute decompensated heart failure and is an important target for therapy. However, achieving complete decongestion can be challenging. Furthermore, residual congestion before discharge from hospital is associated with a high risk of early rehospitalization and death. An improved understanding of the pathophysiology of congestion is of great importance in finding better and more personalized therapies. In this Review, we describe the two different forms of congestion — intravascular congestion and tissue congestion — and hypothesize that differentiating between and specifically treating these two different forms of congestion could improve the outcomes of patients with acute decompensated heart failure. Although the majority of these patients have a combination of both intravascular and tissue congestion, one phenotype can dominate. Each of these two forms of congestion has a different pathophysiology and requires a different diagnostic approach. We provide an overview of novel and established biomarkers, imaging modalities and mechanical techniques for identifying each type of congestion. Treatment with loop diuretics, the current cornerstone of decongestive treatment, reduces circulating blood volume and thereby reduces intravascular congestion. However, the osmolality of the circulating blood decreases with the use of loop diuretics, which might result in less immediate translocation of fluid from the tissues (lungs, abdomen and periphery) to the circulation when the plasma refill rate is exceeded. By contrast, aquaretic drugs (such as vasopressin antagonists) predominantly cause water excretion, which increases the osmolality of the circulating blood, potentially improving translocation of fluid from the tissues to the circulation and thereby relieving tissue congestion.

The treatment of residual congestion is one of the greatest unmet needs in the management of patients with heart failure. Treatment with loop diuretics, the current cornerstone of decongestive treatment, reduces circulating blood volume, and thereby reduces intravascular congestion. However, compared with the use of aquaretic drugs, loop diuretics cause the osmolality of the circulating blood to decrease, which might result in less immediate translocation of fluid from the tissues (lungs, abdomen and periphery) to the circulation when the plasma refill rate is exceeded. A reduced circulating blood volume without the translocation of a similar volume of fluid from the tissues results in neurohormonal activation and possibly worsening of renal function, while patients experience persistent clinical signs and symptoms of (tissue) congestion, such as dyspnoea, rales and peripheral oedema.

In this Review, we focus on the important differences between the two forms of congestion in the intravascular and the tissue interstitial compartments. The difference can be observed at the bedside but the distinction is not routinely made or reported in the literature, where many patients are described as having general congestion. We propose that the distinction between tissue congestion and intravascular congestion is of importance in our understanding and treatment of patients with decompensated heart failure. In particular, we discuss the diagnosis and treatment of tissue congestion versus intravascular congestion in patients with heart failure and the role of natriuresis versus aquaresis.

✉*e-mail:* a.a.voors@umcg.nl

https://doi.org/10.1038/s41569-020-0379-7

Key points

- Congestion is the main reason for hospitalization in patients with acute decompensated heart failure.
- Residual congestion at discharge from hospital is associated with higher rates of death and hospital readmission for heart failure.
- Congestion can be present predominantly in the vascular system (intravascular congestion) or in the interstitium (tissue congestion), although the majority of patients have a combination of both intravascular and tissue congestion.
- Intravascular congestion and tissue congestion can be identified and differentiated with the use of specific diagnostic assessments, such as physical examination, biomarkers and imaging techniques.
- Loop diuretic therapy reduces circulating blood volume, thereby improving intravascular congestion; however, these therapies increase plasma osmolality, which might impede translocation of fluid from the tissues to the circulation.
- Aquaretic drugs, such as vasopressin antagonists, reduce plasma volume and lower plasma osmolality, which might stimulate translocation of fluid from the tissues to the circulation.

Definition, epidemiology and grading

Congestion in heart failure is defined as fluid accumulation in the intravascular compartment and the interstitial space, resulting from increased cardiac filling pressures caused by maladaptive sodium and water retention by the kidneys[1]. Congestion is the main reason for hospitalization in patients with acute (decompensated) heart failure but the severity of congestion varies widely between patients.

In a large, long-term European registry, 83% of all patients admitted to hospital with acute heart failure had clinical signs or symptoms of congestion[2]. A large global cohort study in patients hospitalized for heart failure found that the incidence of peripheral oedema ranged from 39.2% in South-East Asia to 75.2% in Eastern Europe and the incidence of rales ranged from 23.9% in North America to 80.6% in Africa[3].

Clinical congestion scores can be used to assess the degree of congestion. Most clinical congestion scores are a composite of the severity of orthopnoea, jugular vein distension and rales (TABLE 1). Clinical trials targeting congestion in patients with acute heart failure have shown that the incidence of clinically significant congestion (congestion score 3–18) is as high as 97%; however, the inclusion criteria in these trials required a congestion score of ≥1 for enrolment[4,5], thereby excluding patients without signs or symptoms of congestion from the analysis and probably skewing the total incidence of congestion. Approximately 90% of patients with congestion present with symptoms of dyspnoea[4,5] and in the vast majority, if not all, of these patients, loop diuretic therapy is initiated or intensified[6,7].

Incomplete decongestion at discharge from hospital is associated with higher rates of both death and readmission to hospital for heart failure. Patients with residual congestion on day 7 of hospitalization have a more than twofold increase in 180-day mortality and an almost twofold increase in the risk of rehospitalization for heart failure compared with patients without congestion[5].

Tissue versus intravascular congestion

Fluid accumulation leading to decompensated heart failure starts in the intravascular compartment[8]. Continuously increased hydrostatic pressures in the capillary vessels subsequently lead to tissue congestion (FIG. 1). The majority of patients with decompensated heart failure have a combination of both intravascular and tissue congestion, as indicated by the composition of congestion scores (TABLE 1); however, we postulate that one phenotype can dominate. Typical patients with predominant intravascular congestion present with acute-onset high blood pressure, leading to suddenly increased pulmonary and cardiac filling pressures[9,10]. These patients generally respond well to treatment with vasodilators[11,12]. In the heart failure guidelines, these patients are referred to as having the vascular type of congestion[6]. By contrast, patients with predominant tissue congestion present with a gradual increase in cardiac filling pressures and slowly progressive pulmonary, abdominal and peripheral oedema[13]. Moreover, as a result of diuretic treatment, the congestive phenotype can change (that is, intravascular fluid depletion, with residual tissue congestion). We postulate that these different mechanisms of origin of the congestion require different criteria for diagnosis and different approaches to treatment.

Differences in pathophysiology

Intravascular congestion. During an episode of acute decompensated heart failure, a combination of haemodynamic and neurohormonal factors leads to sodium and water retention by the kidneys[1]. These factors are variously present during different stages and severities of heart failure and include low cardiac output, activation of the renin–angiotensin–aldosterone and natriuretic peptide axes, the sympatho-sympathetic reflex as a result of cardiac stretch, and probably other unknown contributors[14]. The relative contributions of these mechanisms vary between patients but most patients with acute heart failure have little or no evidence of cardiogenic shock or low output[15]. Regardless of the cause, the end point of heart failure decompensation is congestion.

Although expansion of plasma volume underlies the congestion in many if not most patients with acute heart failure, endogenous fluid reservoirs can also make

Author addresses

[1]University of Groningen, Department of Cardiology, University Medical Center Groningen, Groningen, Netherlands.
[2]Center for Clinical Medicine, University Faculty of Health, University of Witten Herdecke, Witten, Germany.
[3]Department of Clinical Science, BAYER AG, Research and Development, Wuppertal, Germany.
[4]Department of Cardiology and Clinical Medicine, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.
[5]Department of Medicine, Cardiovascular Division, University of Minnesota, Minneapolis, MN, USA.
[6]Division of Cardiovascular Medicine, Department of Medicine, Hennepin Healthcare, Minneapolis, MN, USA.
[7]Division of Cardiology, Tufts Medical Center, Boston, MA, USA.
[8]Cardiovascular Research Foundation, New York, NY, USA.
[9]Universite de Lorraine, Inserm, Centre d'Investigations Cliniques- Plurithematique 14-33, and Inserm U1116, CHRU, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France.

Table 1 | **Commonly used congestion scores in trials on acute heart failure**

Sign or symptom	Points	EVEREST[135] and EMPA-RESPONSE-AHF[136]	OPTIMIZE-HF[137]	Composite congestion score (EVEREST)[135]	ASCEND-HF[138]	Composite congestion score (PROTECT)[5,72]	Orthoedema score (CARRESS-HF and DOSE-HF)[139]
Peripheral oedema	0	Absent or trace	Absent	Absent	Absent	Absent	Trace
	1	Slight	1+	Slight	Up to shins	Slight	Moderate
	2	Moderate	2+	Moderate	Up to knees	Moderate	Severe
	3	Marked	3+	Marked	Up to sacrum	Marked	–
Orthopnoea	0	None	No	None	No	None	<2 pillows
	1	Seldom	–	2 pillows	–	2 pillows	–
	2	Frequent	Yes	3 pillows	Yes	3 pillows	≥2 pillows
	3	Continuous	–	>30°	–	>30°	–
Dyspnoea	0	None	No	Not included	Not included	Not included	Not included
	1	Seldom	–				
	2	Frequent	On exertion				
	3	Continuous	At rest				
Jugular vein distension (cmH_2O)	0	<6	<6	<6	Not included	<6	Not included
	1	6–9	6–9	6–9		6–10	
	2	10–15	10–15	10–15		>10	
	3	>15	>15	>15		–	
Rales	0	None	None	Not included	Not included	Not included	Not included
	1	Basal	<1/3				
	2	To <50%	>1/3				
	3	To >50%	–				
Fatigue	0	None	No	Not included	Not included	Not included	Not included
	1	Seldom	–				
	2	Frequent	Yes				
	3	Continuous	–				
Plasma NT-proBNP level	1	Not included	Not included	Not included	Tertile 1	Not included	Not included
	2				Tertile 2		
	3				Tertile 3		
Maximum score	–	18	15	9	8	8	4

NT-proBNP, N-terminal pro-B-type natriuretic peptide.

an important contribution, particularly in patients in whom heart failure decompensation develops quickly — that is, in the vascular type of congestion referred to above. The splanchnic veins (the abdominal compartment of the venous circulation) are characterized by a much larger capacity than other veins. The splanchnic veins contain anywhere from 20% to 50% of the total blood volume[16,17]. These veins operate as a functionally sequestered circulation and act as a blood reservoir that can be recruited in the event of hypovolaemia. Another characteristic of the splanchnic veins is a high density of α-adrenergic receptors[18]. In patients with acute heart failure — which is characterized by neurohormonal overactivation — stimulation of α-adrenergic receptors leads to potent venoconstriction and movement of blood from the abdominal compartment to the circulating compartment[18]. This dysregulation of blood distribution has been suggested to have an important role in acute intravascular congestion[19]. Administration of nitroglycerin produces venodilatation and increases the capacity of the splanchnic system, restoring the balance of blood distribution in patients with acute heart failure[18,20]. Therefore, much of the intravascular congestion that occurs in patients with acute heart failure is likely to be a mixture of both a gradual expansion in plasma volume and the shifting of fluid from venous reservoirs, particularly as sympathetic activity increases with symptomatic deterioration.

Tissue congestion. The development of tissue oedema is the result of an imbalance between hydrostatic and oncotic pressures at the level of the interstitium (FIG. 1). In brief, the interstitium contains many glycosaminoglycans (GAGs) branching from one central protein, alongside collagen and elastin fibres. All the GAGs together form a strong network, giving structure to the interstitium.

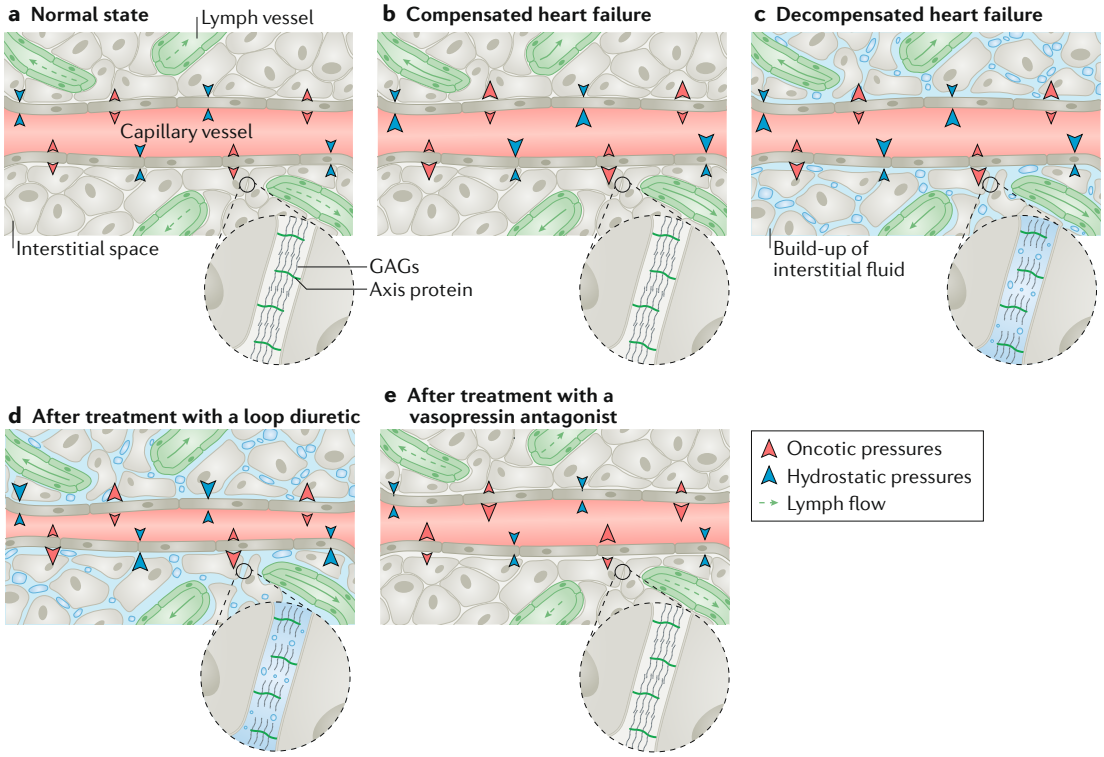


Fig. 1 | **Pathophysiology of tissue congestion. a** | Under normal healthy conditions, hydrostatic pressures and oncotic pressures in the capillary vessel and interstitium are in equilibrium. **b** | During compensated heart failure, hydrostatic pressure in the capillary vessel rises, and oncotic pressure in the capillary vessel decreases. Compensatory mechanisms maintain equilibrium. **c** | During decompensated heart failure, the compensatory mechanisms become insufficient to maintain equilibrium. Hydrostatic pressures in the capillary vessel and oncotic pressures in the interstitium keep increasing. Fluid starts to build up in the interstitial space. The glycosaminoglycan (GAG) networks are no longer bound together. **d** | After treatment with a loop diuretic, hydrostatic pressures in the capillary vessel return to normal, allowing some fluid to re-enter the bloodstream. As a result of natriuresis, osmotic pressure in the capillary vessel also decreases. **e** | After treatment with a vasopressin antagonist, osmotic pressure in the capillary vessel decreases, and residual interstitial fluid re-enters the bloodstream.

The potential clinical relevance and implications of the GAG networks are discussed in BOX 1.

Three protective mechanisms need to be overcome before interstitial fluid can accumulate[8]. First, a slightly lower pressure relative to atmospheric pressure keeps the interstitial GAG networks together. As long as these networks are bound together, a small increase in interstitial pressure will lead to a large increase in hydrostatic pressure in the capillary vessels. At a neutral pressure, when the pressure difference is lost, the force that keeps the GAG networks together no longer exists, providing room for the accumulation of free fluid (that is, water not bound to GAGs). Second, the lymphatic system is highly sensitive to pressure and can increase fluid removal by 10-fold to 50-fold when hydrostatic pressure rises[21]. Third, the lymphatic system drains large amounts of protein, thereby reducing colloid osmotic pressure in the interstitium.

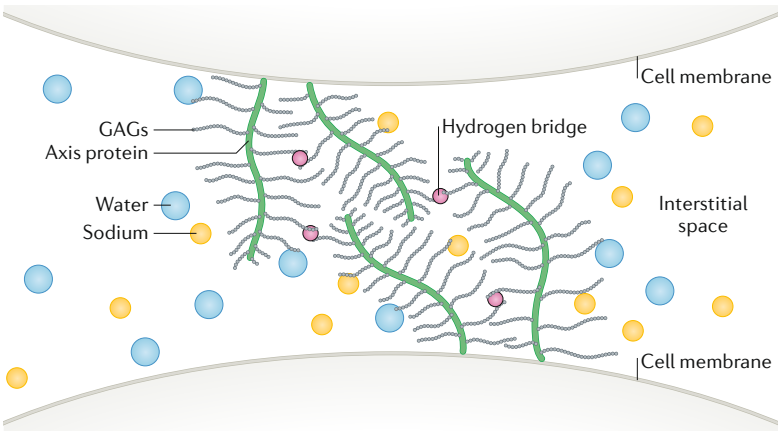
Similar mechanisms are in place in the alveoli. A pulmonary capillary pressure of approximately 28 mmHg, which is 21 mmHg above normal pulmonary capillary pressure, is enough to overcome colloid osmotic pressure in the perialveolar interstitium[22]. In patients with acute left-sided heart failure, minimal surpassing of this threshold is enough to cause life-threatening pulmonary oedema. However, when pulmonary capillary and artery pressures are increased chronically, the diameter and flow in the lymphatic system can gradually increase, and pulmonary artery pressures as high as 45 mmHg without pulmonary oedema have been measured[23].

Conversely, two factors can lower the threshold for the development of oedema. First, long-term sodium saturation of interstitial GAGs changes the form and function of the GAG networks (BOX 1). These changes reduce the integrity of the GAG network so that a slight increase in capillary blood pressure is sufficient to induce oedema. Second, particular comorbidities increase vascular permeability. One condition is diabetes mellitus, probably as a result of the destruction of vascular tissue through the formation of advanced glycation end-products[24,25]. Another situation in which vascular permeability increases is when cytokines are released, such as during inflammation, sepsis or ischaemia[26–28].

The factors described above explain why particular patients with heart failure can have extremely high pulmonary capillary pressures without alveolar congestion, and other patients can develop clinically significant congestion with only slightly increased pulmonary capillary pressures.

Box 1 | **The role of glycosaminoglycans in tissue congestion**

The composition of the interstitium — the space between cells — differs according to the tissue. Nevertheless, the interstitium always contains a so-called ground substance: a gel-like structure composed of proteoglycans. These proteoglycans consist of one axis protein to which many glycosaminoglycans (GAGs) are attached (see the figure). The GAGs from different proteoglycans are in turn connected through various hydrogen bridges. Most of the water molecules in the interstitial space are bound to these GAGs. Small vesicles of free water are present within the gel. Pitting oedema arises when the free water vesicles become larger and can be mobilized between the cells and the interstitial gel. All the GAGs together form a strong network, giving structure to the interstitium. These GAGs are polyanionic and can, therefore, bind large quantities of cations, namely sodium. In doing so, the GAG network has been hypothesized to have an important role in sodium homeostasis and to protect against overt hypernatraemia in heart failure[159]. Furthermore, increases in sodium concentration stimulate gene and protein expression of GAGs[160], increasing the capacity of the GAG network to bind sodium. However, long-term saturation of GAGs with sodium might change their form and function, thereby reducing the integrity of the network as a whole[159,161]. In this situation, a slight increase in capillary blood pressure would be sufficient to induce oedema.



Assessment of intravascular congestion

Currently, the gold standard for assessing intravascular congestion is to measure right atrial pressure (normally 2–6 mmHg) and pulmonary capillary wedge pressure (PCWP; normally 3–8 mmHg) by right heart catheterization[29,30]. However, right heart catheterization is invasive and, therefore, routinely performing this procedure is not attractive. To assess changes in congestion on a day-to-day basis, non-invasive measurements are needed, such as changes in jugular venous pressure, patient-reported symptoms or changes in plasma levels of natriuretic peptides between admission to and discharge from hospital (FIG. 2).

Clinical signs and symptoms

Jugular venous pressure. Distension of the jugular vein provides an indication of right atrial pressure. Historically, this assessment was performed with the jugular venous arch, to measure the distance between the sternal notch and the collapse of the venous column[31]. In current clinical practice, assessment of jugular venous pressure is usually performed by inspection of the jugular veins and estimating the degree of distension[31]. However, precise estimation is difficult, and the sensitivity and specificity for estimating central venous pressure are poor (57.3% and 43.6%, respectively)[32]. Increased jugular venous pressure is indicative of jugular intravascular overfilling and, therefore, we propose that it is a specific sign of intravascular congestion.

Orthopnoea. Orthopnoea is the result of increased venous blood flow from the lower extremities when the patient is in a supine or semi-supine position, which increases cardiac preload that cannot be processed by the failing heart. This sudden, additional preload promotes an increase in the symptoms of dyspnoea. Given that orthopnoea results from increased preload rather than alveolar oedema, we propose that it is a symptom of intravascular congestion rather than tissue congestion.

Third heart sound. The third heart sound is the result of rapid filling of the ventricle in the early part of diastole and rapid deceleration of blood flow in an already-filled ventricle[33]. The sound can occur in healthy children and young adults as a sign of quick heart relaxation. However, the third heart sound can also be heard in patients with cardiac volume overload and systolic dysfunction[34]. Therefore, we consider the third heart sound mainly to be a sign of intravascular (or rather intracardiac) congestion.

Bendopnoea. Bendopnoea is the occurrence of increased dyspnoea when bending forwards and is associated with increased right atrial pressure and PCWP[35]. The presence of bendopnoea correlates with the presence of orthopnoea, exercise intolerance and increased jugular venous pressure but not with rales or peripheral oedema[35,36]. Therefore, bendopnoea seems to be indicative of intravascular congestion rather than of tissue oedema. This notion is supported by the observation that the presence of bendopnoea correlates with more advanced disease in patients with pulmonary arterial hypertension[37].

Biomarkers

Natriuretic peptides. The release of natriuretic peptides into the circulation is induced by increased stretch and/or pressure of the atria and ventricles[38]. Therefore, elevated circulating levels of natriuretic peptides are likely to be an indication of intravascular and intracardiac congestion rather than of tissue congestion. A reduction in the circulating level of natriuretic peptides by ≥30% from hospital admission is generally considered to be an indicator of successful intravascular decongestion and is associated with reductions in jugular vein distension, vena cava diameter and wedge pressure, and mortality[39–41]. Although these findings suggest a role for in-hospital therapy guided by plasma levels of natriuretic peptides, several studies comparing this approach with standard of care found no significant differences in the combined end point of rehospitalization and all-cause death, despite a greater reduction in plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients in the natriuretic peptide-guided treatment group[42,43].

Haemoconcentration. Haemoconcentration, the relative increase in haemoglobin levels in the blood as a result of a reduction in plasma volume, has also been proposed

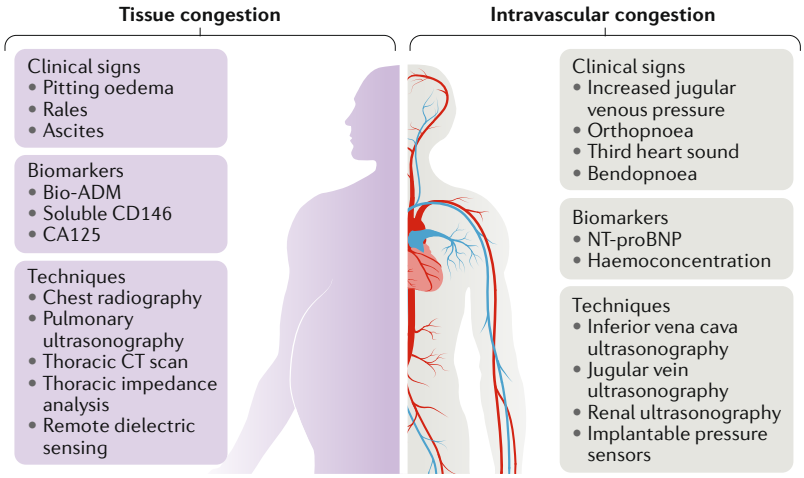


Fig. 2 | **Hypothesized differences between tissue congestion and intravascular congestion.** The figure shows the clinical signs and biomarkers that have been established as markers of congestion and the techniques used for diagnosis. Some signs and biomarkers are more indicative of tissue congestion, whereas others are more indicative of intravascular congestion. bio-ADM, biologically active adrenomedullin; CA125, carbohydrate antigen 125; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

as a marker of decongestion[44,45]. In patients with acute heart failure, haemoconcentration has been associated with clinical signs and symptoms of more aggressive decongestion and improved outcomes, including a lower risk of readmission to hospital for heart failure[46–49]. In one study, patients with haemodilution after initial treatment for acute heart failure had more alveolar oedema and higher body mass at baseline than patients who had haemoconcentration, which indicates translocation of fluid from the tissues to the intravascular space[50]. On the basis of these associations, we conclude that haemoconcentration is a sign of intravascular volume status.

Changes in estimated plasma volume can also be used as a proxy for the plasma refill rate (the rate at which fluid can be transported from the tissue interstitium into the vessels). Given that residual congestion is a predictor of worse outcome, irrespective of the degree of haemoconcentration[49], aiming to maintain haematocrit at a constant level during decongestive treatment has been suggested to decongest at a rate that is equal to the plasma refill rate[44]. For patients undergoing haemodialysis, continuous monitoring of haematocrit levels has been shown to prevent episodes of intradialytic hypotension[51]. To date, this approach has not been examined in patients with heart failure during decongestion treatment.

Imaging and monitoring techniques

Inferior vena cava ultrasonography. Measurement of the inferior vena cava by ultrasonography is an easy method to estimate right atrial pressure. More specifically, a decrease of <50% in the diameter of the inferior vena cava (caval index) during inspiration correlates with a right atrial pressure of ≥10 mmHg (REF.[52]). Increasing inferior vena cava diameters measured in the outpatient setting are predictive of an increased risk of hospitalization and death in patients admitted to hospital for heart failure, and are associated with the presence of clinical signs and symptoms of both tissue and intravascular congestion[53–55].

Jugular vein ultrasonography. Jugular vein ultrasonography might be a more accurate and reproducible measurement than visual inspection of jugular vein distension. This approach has been shown to correlate well with congestive status and to be a predictor of rehospitalization for heart failure[56,57].

Renal ultrasonography. Under normal circumstances, patterns of renal venous flow assessed by ultrasonography are rarely altered by changes in cardiac output[58]. However, patterns of renal venous flow are altered by changes in renal interstitial compliance and increased renal venous pressures[59]. In patients with heart failure, two types of discontinuous renal venous flow patterns can be distinguished: monophasic and biphasic, with patients with monophasic flow having worse outcomes[59]. Patients with discontinuous renal venous flow at baseline, as assessed by ultrasonography, have higher plasma levels of NT-proBNP, higher E/A ratio (a marker of left ventricular function) and more tricuspid valve regurgitation than patients with continuous renal venous flow[58,59]. However, no data are available on the use of renal ultrasonography to assess the presence of residual congestion.

Implantable pressure sensors. Implantable pressure sensors are monitoring devices that can be implanted in the pulmonary artery, where the device continuously monitors pulmonary diastolic pressures. Pulmonary diastolic pressure is used to estimate PCWP, although various formulae for this estimation have been reported[60]. In this way, increases in pulmonary artery pressure can be detected days before clinical signs and symptoms are present, enabling clinicians to make early adjustments to the treatment regimen and thereby avoid the need to hospitalize the patient. Monitoring pulmonary artery pressures in patients with heart failure with the use of an implantable pressure sensor reduces the rate of hospital admission[61,62].

Assessment of tissue congestion

Clinical signs and symptoms

Tissue congestion can be assessed in terms of symptoms and by physical examination, and the established indicators are the presence of rales, ascites and peripheral oedema. Pitting oedema is highly specific for the presence of interstitial oedema[63] but most clinical signs and symptoms have moderate specificity and poor sensitivity for diagnosing heart failure as the cause of interstitial oedema[64]. Tissue congestion can also be assessed with the use of biomarkers and imaging methods (FIG. 2).

Biomarkers

Biologically active adrenomedullin. Adrenomedullin has a prominent role in maintaining the barrier function of the endothelium[65]. The loss of this barrier function results in vascular leakage and subsequently pulmonary and systemic oedema[65]. Accordingly, higher plasma levels of biologically active adrenomedullin are indicative

of increased accumulation of interstitial fluid, and circulating levels of biologically active adrenomedullin are elevated in patients with heart failure[66,67] and particularly in those with sepsis[68] (another condition characterized by massive vascular leakage) compared with healthy individuals. High plasma levels of biologically active adrenomedullin are associated with more severe peripheral oedema and higher jugular venous pressure, the presence of orthopnoea and hepatomegaly, and increased length of hospital stay and all-cause mortality[69,70]. In patients with acute decompensated heart failure, high levels of biologically active adrenomedullin after 7 days of decongestive therapy correlate well with the presence of other clinical signs of residual congestion[67,71,72].

Soluble CD146. Soluble CD146 (also known as cell surface glycoprotein MUC18) is a protein secreted by the vein wall tissue in response to stretch[73]. Plasma levels of soluble CD146 have been found to be higher in patients with heart failure than in healthy controls or patients with non-cardiac dyspnoea[74]. In patients with acute heart failure, higher plasma levels of soluble CD146 correlate with the presence of more clinical signs of congestion and a higher degree of congestion, as assessed by chest radiography[75]. The role of circulating levels of soluble CD146 in predicting hospitalization and assessing decongestion remains to be established.

Carbohydrate antigen 125. Up to two-thirds of patients admitted to hospital for heart failure have elevated plasma levels of carbohydrate antigen 125 (CA125; also known as mucin 16), and elevated levels of CA125 correlate with increased morbidity rates and mortality[76]. CA125 is released by serous tissue (such as the pericardium and pleurae) as a result of mechanical and/or inflammatory stimuli triggered by oedema[77]. Plasma levels of CA125 are higher in patients with peripheral and/or pulmonary oedema and are further elevated in patients with serosal effusion compared with patients with acute heart failure without pronounced serosal effusion[78,79]. In patients with myocardial infarction, increased plasma levels of CA125 predict the onset of heart failure[80]. The CHANCE-HF study[81] examined the use of CA125-guided therapy versus standard of care in patients with acute heart failure and found a lower rate of rehospitalization for acute decompensated heart failure in the CA125-guided group. Of note, patients allocated to the CA125 group were more frequently visited than patients in the standard of care group and received intravenous loop diuretics at home depending on their CA125 levels.

Imaging and monitoring techniques

Chest radiography. Chest radiography can be used to assess the degree of congestion. Radiographic congestion scores correlate well with directly measured mass of lungs obtained from organ donors[82]. Patients with heart failure who are discharged from hospital with higher radiographic congestion scores have higher rates of rehospitalization for heart failure[83]. Interestingly, radiographic congestion scores at hospital admission were not related to patient outcomes in this study[83]. Chest radiography is mostly specific to pulmonary tissue congestion; however, increases in pulmonary vascular width on the chest radiogram are indicative of intravascular congestion because increased pulmonary vascular width correlates well with total blood volume ($r = 0.80$)[84].

Pulmonary ultrasonography. Ultrasonography of the lungs is becoming a generally accepted tool for the evaluation of pulmonary oedema[6,85]. The quantity of water in the lungs corresponds to the degree of echogenicity found on ultrasonography[86]. In the case of interstitial pulmonary oedema, the ultrasound beam is reflected by the oedematous interlobar septa. This situation produces comet-tail reverberation artefacts called B-lines. The number of B-lines is indicative of the degree of pulmonary oedema, with fewer than five B-lines in the complete anterolateral scan (28 regions across the chest) indicating no pulmonary oedema and >30 B-lines indicating severe pulmonary oedema[87]. The number of B-lines correlates moderately well with both PCWP ($r = 0.48$) and the radiographic congestion score ($r = 0.60$)[88]. Moreover, lung ultrasonography can also be used to predict the need for hospitalization for pulmonary oedema in the outpatient setting, with a higher sensitivity than clinical congestion scores, E/e′ ratio and plasma levels of NT-proBNP[89,90]. Thoracic ultrasonography can also be used to identify existing pleural effusion.

Thoracic CT scans. Increased density on high-resolution pulmonary CT scans correlates well with lung weight and has been suggested as a gold standard for the assessment of pulmonary interstitial oedema[91,92].

Thoracic impedance analysis. Bioelectrical impedance analysis is a technique that uses conductance (the inverse of resistance) to estimate the degree of fluid in a body compartment. Transthoracic conduction is measured to estimate pulmonary congestion. In patients with acute heart failure, bioelectrical impedance analysis is a good predictor of length of hospital stay and correlates well with PCWP, plasma levels of natriuretic peptides, E/e′ ratio and the number of B-lines on thoracic ultrasonography[93–95].

Remote dielectric sensing. Remote dielectric sensing is another technique to determine intrathoracic fluid content non-invasively. Unlike the electric currents used in bioelectrical impedance analysis, remote dielectric sensing uses electromagnetic signals, which are less dependent on body habitus and electrode placement. The lungs are predominantly composed of air and water, and dielectric values are highly dependent on the ratio between these two components. No data exist on the degree to which remote dielectric sensing might also be used to detect intravascular congestion. Remote dielectric sensing has been shown to correlate with the degree of pulmonary oedema measured by chest CT and with pulmonary pressures measured during right heart catheterization[96]. Moreover, medical therapy guided by remote dielectric sensing in the months after hospitalization significantly reduced the rate of rehospitalization in an uncontrolled observational study in patients with heart failure[97].

Treatment of congestion

Natriuresis leads to fluid loss because free water passively follows excreted ions in the tubule of the kidney. Loop diuretics make use of this property by blocking the reabsorption of sodium, leading to increased sodium excretion and urine output (FIG. 3). Inhibition of the Na^+–K^+–$2Cl^-$ symporter in the thick ascending limb of the nephron stops the kidney from either diluting or concentrating the urine. Therefore, natriuresis induced by the use of loop diuretics creates tubular fluid that is iso-osmotic to plasma[98]. In some instances, the loss of sodium, potassium and chloride might even decrease the osmolality of the plasma, which prevents interstitial fluid from fully re-entering the bloodstream. Additionally, loop diuretics have a direct effect on the macula densa, leading to renin secretion and a state of further increased neurohormonal activation[99].

An alternative mechanism for producing fluid loss is through direct promotion of the excretion of free water — that is, aquaresis (FIG. 3). Aquaresis decreases urine osmolality and increases blood osmolality and the concentrations of all blood ions. As a result, translocation of fluid from the interstitium to the intravascular space is promoted. The prototypical aquaretic drugs are antagonists of the vasopressin V_2 receptor for arginine vasopressin (also known as antidiuretic hormone). In contrast to loop diuretics, V_2 receptor antagonists do not promote neurohormonal activation and do not lead to worsening renal function[100–102].

Given the different modes of action of aquaretic and natriuretic therapies, aquaretics might have some advantages over loop diuretics in terms of tissue decongestion and avoiding worsening renal function. In FIG. 4, we propose a treatment algorithm on the basis of the presence or absence of tissue and/or intravascular congestion. In brief, we suggest re-evaluating patients soon after initiation of diuretic treatment. The presence of intravascular congestion is likely to prevent the translocation of fluid from the tissues to the intravascular space; therefore, intravascular congestion should be treated first. However, when intravascular congestion is no longer present, but signs and symptoms remain, treatment should be shifted towards fluid translocation, for instance by adding an aquaretic drug. Potential therapies to reduce residual congestion are discussed below.

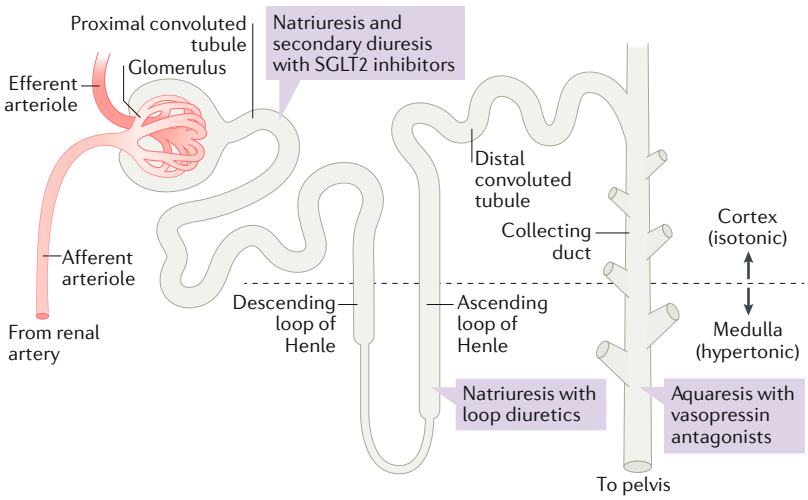


Fig. 3 | **Sites of action of natriuretic and aquaretic drugs in the nephrons.** Inhibitors of the sodium–glucose cotransporter 2 (SGLT2) in the first two-thirds of the proximal convoluted tubule increase the excretion of sodium and glucose and thereby cause secondary diuresis. Loop diuretics inhibit sodium reabsorption via sodium–potassium–chloride cotransporters in the thick ascending limb of the loop of Henle, causing natriuresis. Antagonists of vasopressin V_2 receptors in the collecting duct promote aquaresis.

Increasing natriuresis

Loop diuretics and thiazides. Heart failure guidelines currently recommend the use of loop diuretics and/or thiazide diuretics to reduce the clinical signs and symptoms of congestion in patients with chronic or acute heart failure[6,103], including heart failure with preserved ejection fraction. Reduction of (cardiovascular) mortality with loop diuretics and thiazides has not been proven, but one meta-analysis showed a reduction in the risk of death and worsening heart failure with loop and thiazide diuretic therapies, and these drugs seem to improve exercise capacity[104].

Mineralocorticoid-receptor antagonists. Mineralocorticoid-receptor antagonists inhibit the effects of aldosterone, thereby increasing sodium excretion and potassium retention[105]. The beneficial effects of mineralocorticoid-receptor antagonists on clinical outcomes in patients with chronic heart failure with reduced ejection fraction have been shown in two large randomized clinical trials[106,107]. In patients with left ventricular dysfunction after myocardial infarction, patients receiving 25–50 mg of eplerenone daily had significantly greater reductions in body mass and higher haemoconcentrations than patients receiving placebo, indicating a diuretic effect of eplerenone[108]. However, in the RALES trial[109] in patients with severe chronic heart failure, no increase in natriuresis could be identified in patients receiving 12.5–50.0 mg of spironolactone (equivalent to 25–100 mg of eplerenone)[110]. Conversely, doses of ≥100 mg of spironolactone daily have been shown to increase natriuresis[111,112] but did not lead to better decongestion compared with standard of care in patients with acute heart failure[113].

Acetazolamide. Acetazolamide, a carbonic anhydrase inhibitor, blocks the reabsorption of sodium and bicarbonate in the proximal convoluted tubule, resulting in natriuresis and self-limiting metabolic acidosis. Acetazolamide was a popular diuretic in the 1950s but the use of this drug gradually declined after the introduction of loop diuretics. However, several small studies in patients with heart failure have shown that acetazolamide given in addition to loop diuretics might increase natriuresis compared with the use of loop diuretics alone[114–116].

Fluid redistribution

Vasopressin antagonists: increasing aquaresis. Arginine vasopressin is a hormone secreted by the posterior pituitary gland in response to increased osmolality of the blood. Arginine vasopressin acts on three receptors:

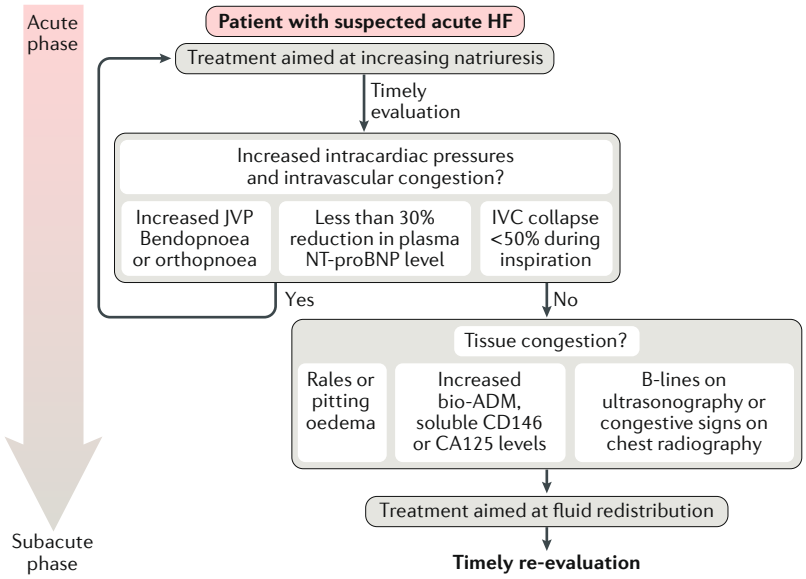


Fig. 4 | **Treatment algorithm for intravascular congestion and tissue congestion.** In patients with acute heart failure (HF), we suggest first treating intravascular congestion with the use of natriuretic drugs. When intravascular congestion is no longer present, but signs and symptoms remain, treatment should be shifted towards fluid translocation, for instance by adding an aquaretic drug. bio-ADM, biologically active adrenomedullin; CA125, carbohydrate antigen 125; IVC, inferior vena cava; JVP, jugular venous pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

V_{1a}, V_{1b} and V_2. Activation of the V_{1a} receptor induces vasoconstriction, increased platelet aggregation and myocyte hypertrophy, whereas the V_{1b} receptor is located in the anterior pituitary and has a role in the cortisol axis. Blockade of V_2 receptors results in decreased expression of aquaporin 2 (the transporter responsible for the greatest amount of water reabsorption in the kidneys) in the late distal tubules and the collecting ducts[8]. Therefore, blocking the effects of vasopressin leads to potent aquaresis. By increasing aquaresis but not natriuresis, intravascular osmotic pressure rises[117], hypothetically allowing fluid to migrate from the interstitium to the vasculature.

The EVEREST trial[4], the first and largest trial on the effects of tolvaptan (a V_2 receptor antagonist) in patients with heart failure, showed no improvement in the dual primary end point of all-cause mortality and cardiovascular death or hospitalization for heart failure with tolvaptan therapy compared with placebo. However, tolvaptan therapy had short-term beneficial effects on dyspnoea, clinical congestion scores and change in body mass and/or net fluid loss in the EVEREST[4] and TACTICS-HF[118] trials. These effects were most pronounced in patients with hyponatraemia, suggesting an important role for the change in plasma osmolality with tolvaptan therapy. Moreover, these patients had no significant changes in blood pressure and only modest changes in filling pressures, and renal function was unchanged or improved over time compared with patients receiving placebo[119]. These findings again support the hypothesis that interstitial fluid translocates into the blood as a result of changes in plasma osmolality. The beneficial effects of tolvaptan therapy on fluid loss and dyspnoea in patients with acute decompensated heart failure have been confirmed in several other studies[100,120,121].

SGLT2 inhibitors: combining natriuresis and increasing osmosis. Sodium–glucose cotransporter 2 (SGLT2) inhibitors cause natriuresis by inhibition of glucose transport, which is driven by concurrent sodium transport in the proximal convoluted tubule in the kidney. Therapy with the SGLT2 inhibitor dapagliflozin has been shown to reduce mortality and hospitalizations for heart failure compared with placebo in patients with heart failure with reduced ejection fraction[122]. Although the mechanism of this benefit remains to be elucidated, natriuretic effects are generally thought to be important[123]. However, one study hypothesized a larger role for aquaresis, suggesting the possibility of using SGLT2 inhibitors in the treatment of tissue congestion, similar to the use of vasopressin antagonists[124]. Outcomes of other trials on the use of SGLT2 inhibitors in patients with heart failure are expected soon (TABLE 2).

Hypertonic saline: increasing osmosis. Infusion of a hypertonic saline solution theoretically increases the osmotic pressure of the intravascular compartment, attracting fluid from both the interstitium and the cells. Moreover, renal flow is thought to increase, which might result in improved availability of diuretic drugs at their site of action: the kidney[125]. Taken together, these effects would result in an increased diuretic response to decongestive therapies. Preliminary data from one group showed an increased reduction in body mass, preserved renal function and reductions in the length of hospital stay, rate of rehospitalization and mortality with the use of hypertonic saline infusion in addition to loop diuretic therapy compared with loop diuretics alone in patients with acute heart failure[126,127]. However, high-quality, blinded, randomized clinical trials have not yet been performed.

Compression therapy: increasing hydrostatic pressure. Compression therapy (multi-layered bandaging, manual lymphatic drainage and/or compression stockings) is advised as the main conservative treatment to improve lymphatic function and venous circulation, for instance in patients with venous insufficiency[128]. However, compression therapy for the reduction of oedema in heart failure is controversial. Concern about increasing cardiac preload and pulmonary pressures has prohibited conclusive advice on the use of this therapy in patients with heart failure[129,130].

Increasing lymphatic flow. Animal studies indicate that olprinone, a phosphodiesterase type 3 inhibitor, increases lymphatic flow in patients with acute heart failure[131].

Splanchnic nerve block. The abdominal vascular compartment is the largest pool of intravascular blood. As a result of sympathetic nerve overactivity in heart failure, vasoconstriction in this compartment forces venous blood to the thoracic compartment[18]. Preliminary data on the ability of splanchnic nerve blockade to interfere with this process showed a decrease in PCWP

Table 2 | **Recent and ongoing trials targeting natriuresis or aquaresis in heart failure**

Trial	Year of publication	Study design	Intervention	Study population (*n*)	Primary end point	Secondary end points[a]	Status	Refs
Natriuresis: combination of loop and thiazide diuretics								
Ng et al.	2013	Retrospective analysis	Metolazone in addition to furosemide versus furosemide single therapy	Acute decompensated HF (242)	Increase in mean hourly urine output ($P=0.383$) and incidence of worsening renal function ($P=0.819$)	Increase in mean net fluid balance ($P=0.048$) and total urine output at 24 h ($P=0.505$) and at 48 h ($P=0.832$)	Completed	140
CLOROTIC	NA	Randomized, controlled	Thiazide diuretics versus placebo, in addition to loop diuretic treatment	Acute decompensated HF (304)	Changes in body mass and dyspnoea VAS	Length of hospital stay, mortality (all-cause and HF) and rehospitalizations (all-cause and HF)	Recruiting	141
Prospective comparison of metolazone versus chlorothiazide for acute decompensated heart failure with diuretic resistance	NA	Randomized, open-label	Oral metolazone 5 mg versus intravenous chlorothiazide 500 mg	Acute decompensated HF with unresponsive and ineffective diuresis (48)	Net urine output at 24 h	Net urine output at 48 h, net fluid balance over 12 h and 24 h, and body mass change after 48 h	Recruiting	142
Natriuresis: mineralocorticoid-receptor antagonists								
ATHENA-HF	2017	Randomized, controlled	High-dose spironolactone (100 mg) versus placebo or low-dose spironolactone (25 mg)	Acute decompensated HF (360)	Decrease in plasma NT-proBNP level from baseline to 96 h (P = NS)	Decrease in clinical congestion score, dyspnoea, increase in net urine output and net body mass change (P = NS for all)	Completed	113
Ferreira et al.	2014	Single-blinded	Spironolactone 50–100 mg versus standard of care	Acute decompensated HF (100)	Proportion of patients free from congestion on day 3 ($P=0.001$)	Change in body mass (P = NS), decrease in plasma NT-proBNP level ($P=0.05$) and proportion of patients receiving oral furosemide on day 3 ($P<0.001$)	Completed	143
Pilot study of natriuretic versus standard doses of mineralocorticoid receptor antagonists in heart failure and loop diuretic resistance in outpatients	NA	Randomized, controlled	Spironolactone 100 mg versus spironolactone 25 mg	Worsening HF (20)	Change in body mass between baseline and day 7	Change in estimated jugular venous pressure on physical examination, change in 6-min walking test, change in dyspnoea VAS and change on Likert scale	Recruitment complete	144
Natriuresis: sodium–glucose cotransporter 2 inhibitors[b]								
DAPA-HF	2019	Randomized, controlled	Dapagliflozin 10 mg versus placebo	Chronic HFrEF (4,744)	Combined rate of worsening HF or cardiovascular death (HR 0.74)	HF hospitalization (HR 0.75), change in KCCQ score (HR 1.18), worsening renal function (HR 0.71) and all-cause mortality (HR 0.83)	Completed	122
EMPA-RESPONSE	NA	Randomized, controlled	Empagliflozin 10 mg versus placebo	Acute decompensated HF (80)	Combination of dyspnoea relief, diuretic response, length of hospital stay and change in plasma NT-proBNP level (P = NS)	Combination of mortality, HF rehospitalizations within 30 days and worsening HF ($P=0.014$)	Completed	136

Table 2 (cont.) | **Recent and ongoing trials targeting natriuresis or aquaresis in heart failure**

Trial	Year of publication	Study design	Intervention	Study population (*n*)	Primary end point	Secondary end points[a]	Status	Refs
Natriuresis: sodium–glucose cotransporter 2 inhibitors[b] (cont.)								
EMPEROR-Reduced and EMPEROR-Preserved	NA	Randomized, controlled	Empagliflozin 10 mg versus placebo	Chronic HFrEF or HFpEF (3,600 and 5,750)	Composite of time to first HF event, HF hospitalizations or death	Adjudicated HF hospitalization, worsening renal function, time to onset of T2DM, change in KCCQ score from baseline	Recruitment complete	145,146
RECEDE-CHF	NA	Randomized, controlled, crossover	Empagliflozin 25 mg versus placebo	Stable HF and T2DM (34)	Net urinary output	Glomerular filtration rate, plasma cystatin C levels and urinary sodium excretion	Recruiting	147
DAPA-Shuttle 1	NA	Randomized, controlled	Dapagliflozin 10 mg versus placebo	Stable HFrEF and T2DM (40)	Change in urinary osmolyte concentration	Concentration of plasma copeptin, tissue sodium content on ^{23}Na-MRI, and changes in muscle and liver lipid content	Recruiting	148
ELSI	NA	Randomized, controlled	Empagliflozin 10 mg versus placebo	Chronic HFmrEF (84)	Lower-leg skin sodium content (^{23}Na-MRI)	Sodium excretion, skin sodium and water content, plasma NT-proBNP level and vascular stiffness	Recruiting	149
ERADICATE-HF	NA	Randomized, controlled	Ertugliflozin 15 mg versus placebo	Chronic HF and T2DM (36)	Fractional excretion of sodium after 1 and 12 weeks	Glomerular filtration rate, effective renal plasma flow and plasma RAAS hormone levels	Recruiting	150
EMPAG-HF	NA	Randomized, controlled	Empagliflozin 25 mg versus placebo	Acute decompensated HF and T2DM (60)	Total urinary output in 5 days	Worsening renal function, worsening HF, liver function and net fluid output	Recruiting	151
EMBRACE-HF	NA	Randomized, controlled	Empagliflozin 10 mg versus placebo	Chronic HF (60)	Change in pulmonary artery diastolic pressure	Changes in other right heart pressures, KCCQ score, 6-min walking test, plasma BNP level and HbA_{1c}	Recruiting	152
EMPULSE	NA	Randomized, controlled	Empagliflozin 10 mg versus placebo	Stabilized, acute decompensated HF (500)	Combination of time to death, HF events, time to first HF event and change in KCCQ	Change >10 points on KCCQ, change in plasma NT-proBNP level, days alive out of hospital, rehospitalization within 30 days and diuretic effect	Recruitment starting	153
Natriuresis: carbonic anhydrase inhibitors								
Kataoka et al.	2019	Observational, prospective	Acetazolamide 250–500 mg intravenous	Acute HF (18) or stable, chronic HF with hypochloraemia (12)	Short-term increase in plasma chloride level ($P = 0.013$) and long-term increase in plasma chloride level ($P < 0.0001$)	Haemoconcentration and worsening renal function (P = NS for both)	Completed	154
Imiela et al.	2017	Randomized, open-label	Acetazolamide dose adjusted to body mass (250–500 mg) intravenous versus standard of care	Acute decompensated HF (20)	Net fluid output and natriuresis over the first 4 days (P = NS for both)	Cumulative fluid balance after 4 days ($P = 0.035$) and presence of dyspnoea on day 4 ($P < 0.001$)	Completed	155

Table 2 (cont.) | **Recent and ongoing trials targeting natriuresis or aquaresis in heart failure**

Trial	Year of publication	Study design	Intervention	Study population (*n*)	Primary end point	Secondary end points[a]	Status	Refs
Natriuresis: carbonic anhydrase inhibitors (cont.)								
ADVOR	NA	Randomized, controlled	Acetazolamide 500 mg intravenous versus placebo	Acute decompensated HF (519)	Decongestion achieved on day 3 without need to escalate treatment	All-cause mortality, HF readmission within 3 months, length of hospital stay and changes in EuroQol-5 score	Recruiting	156
ACETA	NA	Randomized, controlled	Acetazolamide 500 mg intravenous versus placebo	Acute decompensated HF (90)	Diuresis and negative fluid balance	Worsening renal function, inotropic or vasopressor need, arrhythmias, death, plasma bicarbonate levels and plasma BNP levels	Recruiting	157
Aquaresis: vasopressin antagonists								
EVEREST	2007	Randomized, controlled	Tolvaptan 30 mg versus placebo	Acute decompensated HF (4,133)	All-cause mortality (HR 0.98) and composite of cardiovascular mortality and HF hospitalizations (HR 1.04)	Decrease in body mass on day 1 ($P<0.001$), increase in plasma sodium level on day 7 ($P<0.001$), presence of patient-assessed dyspnoea on day 1 ($P<0.001$) and incidence of clinical worsening of HF ($P=0.62$)	Completed	4
AQUAMARINE	2016	Randomized, controlled, open-label	Tolvaptan 15 mg versus standard of care	Acute decompensated HF with impaired renal function (217)	Increase in cumulative urine output over 48 h (mean difference 1,564 ml; $P<0.001$)	Patient-reported dyspnoea after 48 h ($P=0.02$), worsening renal function ($P=$NS), furosemide dose after 48 h ($P<0.001$) and change in plasma BNP level ($P=0.602$)	Completed	158
AVANTI	NA	Randomized, controlled	Pecavaptan 30 mg versus placebo (part A) or versus furosemide (part B)	Acute decompensated HF with incomplete decongestion (414)	Part A: change in body mass and plasma creatinine level. Part B: change in body mass and BUN:creatinine ratio	Incidence of treatment-emergent adverse events (including serious adverse events) and change in augmentation index	Recruiting	134

BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; HF, heart failure; HFmrEF; heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; NA, not applicable; NS, not significant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAAS, renin–angiotensin–aldosterone system; T2DM, type 2 diabetes mellitus; VAS, visual analogue scale. [a]Some trials have additional secondary end points not listed in the table. [b]Given that ≥43 trials to assess sodium–glucose cotransporter 2 inhibitors are ongoing, only selected trials have been included in the table.

and patient-reported symptoms and an increase in cardiac output[19,132].

Extracorporeal blood ultrafiltration. Blood ultrafiltration is performed with a transmembrane pressure gradient in an extracorporeal unit to filter free water directly from the plasma. Several clinical trials have investigated extracorporeal ultrafiltration as an alternative to (loop) diuretic therapy in patients with acute heart failure. All but one trial found that extracorporeal ultrafiltration was superior in terms of reducing the rates of both short-term and long-term rehospitalizations and mortality[133]. Moreover, ultrafiltration resulted in greater net fluid loss than standard of care. However, patients treated with extracorporeal ultrafiltration also had significantly more treatment-related adverse events, such as infection requiring antibiotics and bleeding requiring transfusion[133]. To date, insufficient knowledge about patient selection and adjustment of the filtration rate prohibits the general use of extracorporeal blood ultrafiltration. Guidelines advise the use of extracorporeal ultrafiltration as a bail-out option for residual congestion despite treatment with a combination of diuretics[103].

Future perspectives

Several clinical trials are addressing the clinical unmet need to find better and additive decongestive therapies. Clinical trials published in the past 13 years and ongoing

trials to assess the effect of decongestive therapies on either mortality and hospitalization or end points related to sodium homeostasis or plasma volume measurements are described in TABLE 2. Of particular interest is the AVANTI trial[134] into the use of pecavaptan, a dual V_{1a}–V_2 receptor antagonist, in patients with acute heart failure and incomplete decongestion despite standard therapy including loop diuretics.

Conclusions

Residual congestion is frequently found in patients who are hospitalized for heart failure and is associated with a poor prognosis and a high rate of (short-term) rehospitalization. Therefore, better treatments or the improvement of current therapies are needed to treat residual congestion. An improved understanding of the pathophysiology of congestion will lead to better treatment of these patients with severe symptoms. Intravascular congestion and tissue congestion have important differences. Clinical assessments, biomarkers, emerging technologies and imaging tools can help to distinguish between the presence of predominant intravascular congestion or tissue congestion (FIG. 2). Moreover, we propose that existing and novel therapies have different effects on each type of congestion. Natriuretic drugs can be used to relieve intravascular congestion, whereas residual tissue congestion might be better treated with an aquaretic drug, such as a vasopressin antagonist. Several clinical trials targeting residual congestion are ongoing, and will hopefully improve our understanding and lead to better outcomes and a more personalized approach to the treatment of congestion in heart failure. The main aim of this Review is to lay a foundation for the clinical subdivision of congestion into intravascular congestion and tissue congestion. Further research is needed to confirm this distinction and to test our hypothesis that distinguishing between these two types of congestion can improve clinical outcomes.

Published online: 15 May 2020

1. Martens, P., Nijst, P. & Mullens, W. Current approach to decongestive therapy in acute heart failure. *Curr. Heart Fail. Rep.* **12**, 367–378 (2015).
2. Chioncel, O. et al. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *Eur. J. Heart Fail.* **19**, 1242–1254 (2017).
3. Filippatos, G. et al. Global differences in characteristics, precipitants, and initial management of patients presenting with acute heart failure. *JAMA Cardiol.* **5**, 401–410 (2020).
4. Konstam, M. A. et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial. *JAMA* **297**, 1319–1331 (2007).
5. Rubio-Gracia, J. et al. Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure. *Int. J. Cardiol.* **258**, 185–191 (2018).
6. Ponikowski, P. et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur. Heart J.* **37**, 2129–2200 (2016).
7. Felker, G. M. et al. Diuretic strategies in patients with acute decompensated heart failure. *N. Engl. J. Med.* **364**, 797–805 (2011).
8. Hall, J. E. in *Guyton and Hall Textbook of Medical Physiology* 296–300 (Saunders, 2011).
9. Viau, D. M., Sala-Mercado, J. A., Spranger, M. D., O'Leary, D. S. & Levy, P. D. The pathophysiology of hypertensive acute heart failure. *Heart* **101**, 1861–1867 (2015).
10. Liu, J. X., Uppal, S. & Patel, V. Management of acute hypertensive heart failure. *Heart Fail. Clin.* **15**, 565–574 (2019).
11. Cotter, G. et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. *Lancet* **351**, 389–393 (1998).
12. Levy, P. et al. Treatment of severe decompensated heart failure with high-dose intravenous nitroglycerin: a feasibility and outcome analysis. *Ann. Emerg. Med.* **50**, 144–152 (2007).
13. Gheorghiade, M. et al. Congestion is an important diagnostic and therapeutic target in heart failure. *Rev. Cardiovasc. Med.* **7** (Suppl. 1), S12–S24 (2006).
14. Zucker, I. H. et al. The origin of sympathetic outflow in heart failure: the roles of angiotensin II and nitric oxide. *Prog. Biophys. Mol. Biol.* **84**, 217–232 (2004).
15. Nohria, A. et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J. Am. Coll. Cardiol.* **41**, 1797–1804 (2003).
16. Burkhoff, D. & Tyberg, J. V. Why does pulmonary venous pressure rise after onset of LV dysfunction: a theoretical analysis. *Am. J. Physiol.* **265**, H1819–H1828 (1993).
17. Fallick, C., Sobotka, P. A. & Dunlap, M. E. Sympathetically mediated changes in capacitance: redistribution of the venous reservoir as a cause of decompensation. *Circ. Heart Fail.* **4**, 669–675 (2011).
18. Gelman, S. Venous function and central venous pressure: a physiologic story. *Anesthesiology* **108**, 735–748 (2008).
19. Fudim, M. et al. Splanchnic nerve block for acute heart failure. *Circulation* **138**, 951–953 (2018).
20. Morse, M. A. & Rutlen, D. L. Influence of nitroglycerin on splanchnic capacity and splanchnic capacity-cardiac output relationship. *J. Appl. Physiol.* **76**, 112–119 (1994).
21. Schmid-Schönbein, G. W. Microlymphatics and lymph flow. *Physiol. Rev.* **70**, 987–1028 (1990).
22. Guyton, A. C. et al. Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. *Circ. Res.* **7**, 649–657 (1959).
23. Haworth, S. G., Hall, S. M. & Patel, M. Peripheral pulmonary vascular and airway abnormalities in adolescents with rheumatic mitral stenosis. *Int. J. Cardiol.* **18**, 405–416 (1988).
24. Hommel, E., Mathiesen, E. R., Aukland, K. & Parving, H. H. Pathophysiological aspects of edema formation in diabetic nephropathy. *Kidney Int.* **38**, 1187–1192 (1990).
25. Bollinger, A. et al. Patterns of diffusion through skin capillaries in patients with long-term diabetes. *N. Engl. J. Med.* **307**, 1305–1310 (1982).
26. Henri, O. et al. Selective stimulation of cardiac lymphangiogenesis reduces myocardial edema and fibrosis leading to improved cardiac function following myocardial infarction. *Circulation* **133**, 1484–1497 (2016).
27. Weis, S. M. & Cheresh, D. A. Pathophysiological consequences of VEGF-induced vascular permeability. *Nature* **437**, 497–504 (2005).
28. Li, J. et al. VEGF, flk-1, and flt-1 expression in a rat myocardial infarction model of angiogenesis. *Am. J. Physiol.* **270**, H1803–H1811 (1996).
29. Binanay, C. et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA* **294**, 1625–1633 (2005).
30. Gheorghiade, M. et al. Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur. J. Heart Fail.* **12**, 423–433 (2010).
31. van't Laar, A. Why is the measurement of jugular venous pressure discredited? *Neth. J. Med.* **61**, 268–272 (2003).
32. Breidthardt, T. et al. How accurate is clinical assessment of neck veins in the estimation of central venous pressure in acute heart failure? Insights from a prospective study. *Eur. J. Heart Fail.* **20**, 1160–1162 (2018).
33. Wynne, J. The clinical meaning of the third heart sound. *Am. J. Med.* **111**, 157–158 (2001).
34. Ramani, S. & Weber, B. N. Detecting the gallop: the third heart sound and its significance. *Med. J. Aust.* **206**, 198–199 (2017).
35. Thibodeau, J. T. et al. Characterization of a novel symptom of advanced heart failure: bendopnea. *JACC Heart Fail.* **2**, 24–31 (2014).
36. Baeza-Trinidad, R., Mosquera-Lozano, J. D., Gómez-Del Mazo, M. & Ariño-Pérez de Zabalza, I. Evolution of bendopnea during admission in patients with decompensated heart failure. *Eur. J. Intern. Med.* **51**, e23–e24 (2018).
37. Karauzum, K. et al. Bendopnea and its clinical importance in outpatient patients with pulmonary arterial hypertension. *Acta Cardiol. Sin.* **34**, 518–525 (2018).
38. Levin, E. R., Gardner, D. G. & Samson, W. K. Natriuretic peptides. *N. Engl. J. Med.* **339**, 321–328 (1998).
39. Omar, H. R. & Guglin, M. Clinical and prognostic significance of positive hepatojugular reflux on discharge in acute heart failure: insights from the ESCAPE trial. *Biomed. Res. Int.* **2017**, 5734749 (2017).
40. Beltrami, M. et al. Different trajectories and significance of B-type natriuretic peptide, congestion and acute kidney injury in patients with heart failure. *Intern. Emerg. Med.* **12**, 593–603 (2017).
41. Francis, G. S., Felker, G. M. & Tang, W. H. W. A test in context: critical evaluation of natriuretic peptide testing in heart failure. *J. Am. Coll. Cardiol.* **67**, 330–337 (2016).
42. Stienen, S. et al. NT-proBNP (N-terminal pro-B-type natriuretic peptide)-guided therapy in acute decompensated heart failure: PRIMA II randomized controlled trial (Can NT-ProBNP-guided therapy during hospital admission for acute decompensated heart failure reduce mortality and readmissions?). *Circulation* **137**, 1671–1683 (2018).
43. Felker, G. M. et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* **318**, 713–720 (2017).
44. Boyle, A. & Sobotka, P. A. Redefining the therapeutic objective in decompensated heart failure: hemoconcentration as a surrogate for plasma refill rate. *J. Card. Fail.* **12**, 247–249 (2006).
45. Testani, J. M., Chen, J., McCauley, B. D., Kimmel, S. E. & Shannon, R. P. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation* **122**, 265–272 (2010).
46. Ter Maaten, J. M. et al. Combining diuretic response and hemoconcentration to predict rehospitalization after admission for acute heart failure. *Circ. Heart Fail.* **9**, e002845 (2016).

47. van der Meer, P. et al. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. *J. Am. Coll. Cardiol.* **61**, 1973–1981 (2013).
48. Davila, C., Reyentovich, A. & Katz, S. D. Clinical correlates of hemoconcentration during hospitalization for acute decompensated heart failure. *J. Card. Fail.* **17**, 1018–1022 (2011).
49. Grau Amorós, J. et al. Hemoconcentration as a prognostic factor after hospital discharge in acute heart failure in the RICA registry. *Rev. Clin. Esp.* **219**, 1–9 (2019).
50. Fujita, T. et al. Hemodilution after initial treatment in patients with acute decompensated heart failure. *Int. Heart J.* **59**, 573–579 (2018).
51. Schroeder, K. L., Sallustio, J. E. & Ross, E. A. Continuous haematocrit monitoring during intradialytic hypotension: precipitous decline in plasma refill rates. *Nephrol. Dial. Transplant.* **19**, 652–656 (2004).
52. Kircher, B. J., Himelman, R. B. & Schiller, N. B. Noninvasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava. *Am. J. Cardiol.* **66**, 493–496 (1990).
53. Khandwalla, R. M. et al. Usefulness of serial measurements of inferior vena cava diameter by VscanTM to identify patients with heart failure at high risk of hospitalization. *Am. J. Cardiol.* **119**, 1631–1636 (2017).
54. Jobs, A. et al. Inferior vena cava diameter in acute decompensated heart failure as predictor of all-cause mortality. *Heart Vessel.* **32**, 856–864 (2017).
55. Pellicori, P. et al. Prevalence, pattern and clinical relevance of ultrasound indices of congestion in outpatients with heart failure. *Eur. J. Heart Fail.* **21**, 904–916 (2019).
56. Pellicori, P. et al. Revisiting a classical clinical sign: jugular venous ultrasound. *Int. J. Cardiol.* **170**, 364–370 (2014).
57. Pellicori, P. et al. Prognostic significance of ultrasound-assessed jugular vein distensibility in heart failure. *Heart* **101**, 1149–1158 (2015).
58. Nijst, P., Martens, P., Dupont, M., Tang, W. H. W. & Mullens, W. Intrarenal flow alterations during transition from euvolemia to intravascular volume expansion in heart failure patients. *JACC Heart Fail.* **5**, 672–681 (2017).
59. Iida, N. et al. Clinical implications of intrarenal hemodynamic evaluation by Doppler ultrasonography in heart failure. *JACC Heart Fail.* **4**, 674–682 (2016).
60. Handoko, M. L. et al. A critical appraisal of transpulmonary and diastolic pressure gradients. *Physiol. Rep.* **4**, e12910 (2016).
61. Assaad, M., Sarsam, S., Naqvi, A. & Zughaib, M. CardioMems® device implantation reduces repeat hospitalizations in heart failure patients: a single center experience. *JRSM Cardiovasc. Dis.* **8**, 2048004019833290 (2019).
62. Givertz, M. M. et al. Pulmonary artery pressure-guided management of patients with heart failure and reduced ejection fraction. *J. Am. Coll. Cardiol.* **70**, 1875–1886 (2017).
63. Kumar, V., Abbas, A. K. & Aster, J. C. *Robbins and Cotran Pathologic Basis of Disease* (Saunders, 2010).
64. Kelder, J. C. et al. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. *Circulation* **124**, 2865–2873 (2011).
65. Koyama, T. et al. Vascular endothelial adrenomedullin-RAMP2 system is essential for vascular integrity and organ homeostasis. *Circulation* **127**, 842–853 (2013).
66. Voors, A. A. et al. Adrenomedullin in heart failure: pathophysiology and therapeutic application. *Eur. J. Heart Fail.* **21**, 163–171 (2019).
67. Tolppanen, H. et al. Adrenomedullin: a marker of impaired hemodynamics, organ dysfunction, and poor prognosis in cardiogenic shock. *Ann. Intensive Care* **7**, 6 (2017).
68. Caironi, P. et al. Circulating biologically active adrenomedullin (bio-ADM) predicts hemodynamic support requirement and mortality during sepsis. *Chest* **152**, 312–320 (2017).
69. Molvin, J. et al. Bioactive adrenomedullin, proenkephalin A and clinical outcomes in an acute heart failure setting. *Open Heart* **6**, e001048 (2019).
70. Ter Maaten, J. M. et al. Bio-adrenomedullin as a marker of congestion in patients with new-onset and worsening heart failure. *Eur. J. Heart Fail.* **21**, 732–743 (2019).
71. Arrigo, M., Parenica, J., Ganovska, E., Pavlusova, M. & Mebazaa, A. Plasma bio-adrenomedullin is a marker of acute heart failure severity in patients with acute coronary syndrome. *Int. J. Cardiol. Heart Vasc.* **22**, 174–176 (2019).
72. Pandhi, P. et al. Clinical value of pre-discharge bio-adrenomedullin as a marker of residual congestion and high risk of heart failure hospital readmission. *Eur. J. Heart Fail.* **22**, 683–691 (2020).
73. Arrigo, M. et al. Soluble CD146 is a novel marker of systemic congestion in heart failure patients: an experimental mechanistic and transcardiac clinical study. *Clin. Chem.* **63**, 386–393 (2017).
74. Van Aelst, L. N. L. et al. Acutely decompensated heart failure with preserved and reduced ejection fraction present with comparable haemodynamic congestion. *Eur. J. Heart Fail.* **20**, 738–747 (2018).
75. Kubena, P. et al. Plasma levels of soluble CD146 reflect the severity of pulmonary congestion better than brain natriuretic peptide in acute coronary syndrome. *Ann. Lab. Med.* **36**, 300–305 (2016).
76. Núñez, J. et al. Clinical utility of antigen carbohydrate 125 in heart failure. *Heart Fail. Rev.* **19**, 575–584 (2014).
77. de la Espriella-Juan, R., Núñez, J., Núñez, E., Sanchis, J. & Bayés-Genis, A. Carbohydrate antigen-125 in heart failure: an overlooked biomarker of congestion. *JACC Heart Fail.* **6**, 441–442 (2018).
78. Kouris, N. T. et al. The significance of CA125 levels in patients with chronic congestive heart failure. Correlation with clinical and echocardiographic parameters. *Eur. J. Heart Fail.* **7**, 199–203 (2005).
79. Durak-Nalbantic, A. et al. Serum level of tumor marker carbohydrate antigen-CA125 in heart failure. *Med. Arch.* **67**, 241–244 (2013).
80. Falcão, F. J. A. et al. Carbohydrate antigen 125 predicts pulmonary congestion in patients with ST-segment elevation myocardial infarction. *Braz. J. Med. Biol. Res.* **52**, e9124 (2019).
81. Núñez, J. et al. Carbohydrate antigen-125-guided therapy in acute heart failure: CHANCE-HF: a randomized study. *JACC Heart Fail.* **4**, 833–843 (2016).
82. Ware, L. B. et al. Comparison of chest radiograph scoring to lung weight as a quantitative index of pulmonary edema in organ donors. *Clin. Transpl.* **26**, 665–671 (2012).
83. Kobayashi, M. et al. Mid-term prognostic impact of residual pulmonary congestion assessed by radiographic scoring in patients admitted for worsening heart failure. *Int. J. Cardiol.* **289**, 91–98 (2019).
84. Pistolesi, M., Milne, E. N., Miniati, M. & Giuntini, C. The vascular pedicle of the heart and the vena azygos. Part II: Acquired heart disease. *Radiology* **152**, 9–17 (1984).
85. Collins, S. P. et al. Clinical and research considerations for patients with hypertensive acute heart failure: a consensus statement from the Society for Academic Emergency Medicine and the Heart Failure Society of America Acute Heart Failure Working Group. *Acad. Emerg. Med.* **23**, 922–931 (2016).
86. Martindale, J. L. et al. Diagnosing acute heart failure in the emergency department: a systematic review and meta-analysis. *Acad. Emerg. Med.* **23**, 223–242 (2016).
87. Picano, E. & Pellikka, P. A. Ultrasound of extravascular lung water: a new standard for pulmonary congestion. *Eur. Heart J.* **37**, 2097–2104 (2016).
88. Gargani, L. Lung ultrasound: a new tool for the cardiologist. *Cardiovasc. Ultrasound* **9**, 6 (2011).
89. Miglioranza, M. H. et al. Pulmonary congestion evaluated by lung ultrasound predicts decompensation in heart failure outpatients. *Int. J. Cardiol.* **240**, 271–278 (2017).
90. Miglioranza, M. H. et al. Lung ultrasound for the evaluation of pulmonary congestion in outpatients: a comparison with clinical assessment, natriuretic peptides, and echocardiography. *JACC Cardiovasc. Imaging* **6**, 1141–1151 (2013).
91. Gattinoni, L., Caironi, P., Pelosi, P. & Goodman, L. R. What has computed tomography taught us about the acute respiratory distress syndrome? *Am. J. Respir. Crit. Care Med.* **164**, 1701–1711 (2001).
92. Brasileiro, F. C. et al. High-resolution CT scan in the evaluation of exercise-induced interstitial pulmonary edema in cardiac patients. *Chest* **111**, 1577–1582 (1997).
93. Massari, F. et al. Bioimpedance vector analysis predicts hospital length of stay in acute heart failure. *Nutrition* **61**, 56–60 (2019).
94. Génot, N. et al. Bioelectrical impedance analysis for heart failure diagnosis in the ED. *Am. J. Emerg. Med.* **33**, 1025–1029 (2015).
95. Facchini, C. et al. Lung ultrasound and transthoracic impedance for noninvasive evaluation of pulmonary congestion in heart failure. *J. Cardiovasc. Med.* **17**, 510–517 (2016).
96. Amir, O. et al. Validation of remote dielectric sensing (ReDS™) technology for quantification of lung fluid status: comparison to high resolution chest computed tomography in patients with and without acute heart failure. *Int. J. Cardiol.* **221**, 841–846 (2016).
97. Amir, O. et al. Evaluation of remote dielectric sensing (ReDS) technology-guided therapy for decreasing heart failure re-hospitalizations. *Int. J. Cardiol.* **240**, 279–284 (2017).
98. Koeppen, B. M. & Stanton, B. A. *Renal Physiology* (Elsevier, 2019).
99. Yu, A. S. L. et al. in *Brenner and Rector's The Kidney* 1708–1740 (Elsevier, 2020).
100. Udelson, J. E. et al. A multicenter, randomized, double-blind, placebo-controlled study of tolvaptan monotherapy compared to furosemide and the combination of tolvaptan and furosemide in patients with heart failure and systolic dysfunction. *J. Card. Fail.* **17**, 973–981 (2011).
101. Zimmer, C. A. et al. Vasopressin-2-receptor antagonism augments water excretion without changes in renal hemodynamics or sodium and potassium excretion in human heart failure. *Am. J. Physiol.* **290**, F273–F278 (2006).
102. Veeraveedu, P. T. et al. Effects of V2-receptor antagonist tolvaptan and the loop diuretic furosemide in rats with heart failure. *Biochem. Pharmacol.* **75**, 1322–1330 (2008).
103. Yancy, C. W. et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J. Am. Coll. Cardiol.* **70**, 776–803 (2017).
104. Faris, R. F., Flather, M., Purcell, H., Poole-Wilson, P. A. & Coats, A. J. S. Diuretics for heart failure. *Cochrane Database Syst. Rev.* **2**, CD003838 (2012).
105. Masoumi, A., Ortiz, F., Radhakrishnan, J., Schrier, R. & Colombo, P. Mineralocorticoid receptor antagonists as diuretics: can congestive heart failure learn from liver failure? *Heart Fail. Rev.* **20**, 283–290 (2015).
106. Zannad, F. et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N. Engl. J. Med.* **364**, 11–21 (2011).
107. Pitt, B. et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N. Engl. J. Med.* **341**, 709–717 (1999).
108. Rossignol, P. et al. Eplerenone survival benefits in heart failure patients post-myocardial infarction are independent from its diuretic and potassium-sparing effects. Insights from an EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) substudy. *J. Am. Coll. Cardiol.* **58**, 1958–1966 (2011).
109. Rales Investigators. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). *Am. J. Cardiol.* **78**, 902–907 (1996).
110. Struthers, A., Krum, H. & Williams, G. H. A comparison of the aldosterone-blocking agents eplerenone and spironolactone. *Clin. Cardiol.* **31**, 153–158 (2008).
111. Kapelios, C. J. et al. Association between high-dose spironolactone and decongestion in patients with acute heart failure: an observational retrospective study. *Am. J. Cardiovasc. Drugs* **18**, 415–422 (2018).
112. Hensen, J., Abraham, W. T., Dürr, J. A. & Schrier, R. W. Aldosterone in congestive heart failure: analysis of determinants and role in sodium retention. *Am. J. Nephrol.* **11**, 441–446 (1991).
113. Butler, J. et al. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. *JAMA Cardiol.* **2**, 950–958 (2017).
114. Verbrugge, F. H. et al. Acetazolamide to increase natriuresis in congestive heart failure at high risk for diuretic resistance. *Eur. J. Heart Fail.* **21**, 1415–1422 (2019).
115. Wongboonsin, J. et al. Acetazolamide therapy in patients with heart failure: a meta-analysis. *J. Clin. Med.* **8**, E349 (2019).
116. Mullens, W. et al. Rationale and design of the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial. *Eur. J. Heart Fail.* **20**, 1591–1600 (2018).

117. Shoaf, S. E., Bricmont, P. & Mallikaarjun, S. Pharmacokinetics and pharmacodynamics of oral tolvaptan in patients with varying degrees of renal function. *Kidney Int.* **85**, 953–961 (2014).
118. Felker, G. M. et al. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. *J. Am. Coll. Cardiol.* **69**, 1399–1406 (2017).
119. Cavalcante, J. L., Khan, S. & Gheorghiade, M. EVEREST study: efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan. *Expert. Rev. Cardiovasc. Ther.* **6**, 1331–1338 (2008).
120. Konstam, M. A. et al. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. *J. Am. Coll. Cardiol.* **69**, 1409–1419 (2017).
121. Matsue, Y. et al. Early treatment with tolvaptan improves diuretic response in acute heart failure with renal dysfunction. *Clin. Res. Cardiol.* **106**, 802–812 (2017).
122. McMurray, J. J. V. et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N. Engl. J. Med.* **381**, 1995–2008 (2019).
123. Lytvyn, Y., Bjornstad, P., Udell, J. A., Lovshin, J. A. & Cherney, D. Z. I. Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. *Circulation* **136**, 1643–1658 (2017).
124. Hallow, K. M., Helmlinger, G., Greasley, P. J., McMurray, J. J. V. & Boulton, D. W. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. *Diabetes Obes. Metab.* **20**, 479–487 (2018).
125. Paterna, S. et al. Hypertonic saline in conjunction with high-dose furosemide improves dose–response curves in worsening refractory congestive heart failure. *Adv. Ther.* **32**, 971–982 (2015).
126. Wan, Y. et al. Impact of compound hypertonic saline solution on decompensated heart failure. *Int. Heart J.* **58**, 601–607 (2017).
127. Gandhi, S., Mosleh, W. & Myers, R. B. H. Hypertonic saline with furosemide for the treatment of acute congestive heart failure: a systematic review and meta-analysis. *Int. J. Cardiol.* **173**, 139–145 (2014).
128. Executive Committee. The diagnosis and treatment of peripheral lymphedema: 2016 Consensus Document of the International Society of Lymphology. *Lymphology* **49**, 170–184 (2016).
129. Leduc, O. et al. Impact of manual lymphatic drainage on hemodynamic parameters in patients with heart failure and lower limb edema. *Lymphology* **44**, 13–20 (2011).
130. Wilputte, F. et al. Hemodynamic response to multilayered bandages dressed on a lower limb of patients with heart failure. *Eur. J. Lymphol. Relat. Probl.* **15**, 1–4 (2005).
131. Tomoyasu, M. et al. Effect of phosphodiesterase III inhibitor (Olprinone) on thoracic duct lymph flow in anesthetized sheep with experimentally induced heart failure by endothelin-1. *Lymphology* **35**, 144–152 (2002).
132. Fudim, M. et al. Splanchnic nerve block for decompensated chronic heart failure: splanchnic-HF. *Eur. Heart J.* **39**, 4255–4256 (2018).
133. Costanzo, M. R. et al. Extracorporeal ultrafiltration for fluid overload in heart failure current status and prospects for further research. *J. Am. Coll. Cardiol.* **69**, 2428–2445 (2017).
134. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03901729 (2020).
135. Ambrosy, A. P. et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur. Heart J.* **34**, 835–843 (2013).
136. Damman, K. et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). *Eur. J. Heart Fail.* **22**, 713–722 (2020).
137. Cooper, L. B. et al. The burden of congestion in patients hospitalized with acute decompensated heart failure. *Am. J. Cardiol.* **124**, 545–553 (2019).
138. Masson, R. et al. A novel in-hospital congestion score to risk stratify patients admitted for worsening heart failure (from ASCEND-HF). *J. Cardiovasc. Transl. Res.* https://doi.org/10.1007/s12265-020-09954-x (2020).
139. Lala, A. et al. Relief and recurrence of congestion during and after hospitalization for acute heart failure: insights from diuretic optimization strategy evaluation in acute decompensated heart failure (DOSE-AHF) and cardiorenal rescue study in acute decompensated heart failure (CARESS-HF). *Circ. Heart Fail.* **8**, 741–748 (2015).
140. Ng, T. M. H. et al. Comparison of bumetanide- and metolazone-based diuretic regimens to furosemide in acute heart failure. *J. Cardiovasc. Pharmacol. Ther.* **18**, 345–353 (2013).
141. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT01647932 (2019).
142. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03574857 (2018).
143. Ferreira, J. P. et al. Mineralocorticoid receptor antagonism in acutely decompensated chronic heart failure. *Eur. J. Intern. Med.* **25**, 67–72 (2014).
144. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02585843 (2019).
145. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03057951 (2020).
146. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03057977 (2020).
147. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03226457 (2019).
148. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT04080518 (2020).
149. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03128528 (2020).
150. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03416270 (2018).
151. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT04049045 (2019).
152. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03030222 (2020).
153. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT04157751 (2020).
154. Kataoka, H. Acetazolamide as a potent chloride-regaining diuretic: short- and long-term effects, and its pharmacologic role under the 'chloride theory' for heart failure pathophysiology. *Heart Vessel.* **34**, 1952–1960 (2019).
155. Imiela, T. & Budaj, A. Acetazolamide as add-on diuretic therapy in exacerbations of chronic heart failure: a pilot study. *Clin. Drug Investig.* **37**, 1175–1181 (2017).
156. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03505788 (2019).
157. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03720288 (2018).
158. Matsue, Y. et al. Clinical effectiveness of tolvaptan in patients with acute heart failure and renal dysfunction. *J. Card. Fail.* **22**, 423–432 (2016).
159. Nijst, P. et al. The pathophysiological role of interstitial sodium in heart failure. *J. Am. Coll. Cardiol.* **65**, 378–388 (2015).
160. Heer, M. et al. Increasing sodium intake from a previous low or high intake affects water, electrolyte and acid–base balance differently. *Br. J. Nutr.* **101**, 1286–1294 (2009).
161. Wolff, J. J., Laremore, T. N., Busch, A. M., Linhardt, R. J. & Amster, I. J. Influence of charge state and sodium cationization on the electron detachment dissociation and infrared multiphoton dissociation of glycosaminoglycan oligosaccharides. *J. Am. Soc. Mass. Spectrom.* **19**, 790–798 (2008).

Author contributions

E.M.B. researched data for the article. E.M.B., J.M.t.M., K.D., S.G., F.Z. and A.A.V. discussed the content of the article. E.M.B. wrote the manuscript, and all the other authors reviewed and edited the manuscript before submission.

Competing interests

W.D. reports full-time employment at Bayer. F.G. receives advisor fees from Abbott, Bayer, Carmat, Impulse Dynamics, Novartis and Pfizer and speaker fees from AstraZeneca, Boehringer Ingelheim and Orion Pharma. S.G. has received consultancy fees and/or research grants from Abbott Laboratories, Bayer and Otsuka Pharmaceuticals. J.E.U. reports research funding for trial activities from Bayer. A.A.V. has received consultancy fees and/or research grants from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Myokardia, Novartis and Roche Diagnostics. The other authors declare no competing interests.

Peer review information

Nature Reviews Cardiology thanks R. Mentz and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.