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Organ dysfunction, injury and failure in acute heart failure: from pathophysiology to diagnosis and management. A review on behalf of the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)

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Abstract

Organ injury and impairment are commonly observed in patients with acute heart failure (AHF), and congestion is an essential pathophysiological mechanism of impaired organ function. Congestion is the predominant clinical profile in most patients with AHF; a smaller proportion presents with peripheral hypoperfusion or cardiogenic shock. Hypoperfusion further deteriorates organ function. The injury and dysfunction of target organs (i.e. heart, lungs, kidneys, liver, intestine, brain) in the setting of AHF are associated with increased risk for mortality. Improvement in organ function after decongestive therapies has been associated with a lower risk for post-discharge mortality. Thus, the prevention and correction of organ dysfunction represent a therapeutic target of interest in AHF and should be evaluated in clinical trials. Treatment strategies that specifically prevent, reduce or reverse organ dysfunction remain to be identified and evaluated

to determine if such interventions impact mortality, morbidity and patient-centred outcomes. This paper reflects current understanding among experts of the presentation and management of organ impairment in AHF and suggests priorities for future research to advance the field.

Keywords

Heart failure; Multiple organ failure; Venous congestion

Introduction

Acute heart failure (AHF) is characterized by an acute or subacute deterioration in cardiac function resulting from numerous possible underlying heart diseases and precipitating factors.[1] Congestion is the predominant clinical profile in most patients with AHF; a smaller proportion presents with peripheral hypoperfusion or cardiogenic shock.[1–3] Congestion or hypoperfusion can lead to organ injury, impairment and, ultimately, the failure of target organs (i.e. heart, lungs, kidneys, liver, intestine, brain), which are associated with increased mortality. Data suggest that the correction and prevention of organ injury are associated with better outcomes.[4] Thus, the prevention and correction of organ dysfunction have evolved as therapeutic targets of interest in AHF and should be further evaluated in clinical trials.[5]

The pathophysiology behind organ injury in AHF remains incompletely understood. Elderly patients with comorbidities are especially predisposed to organ injury.[6] Treatment strategies that prevent, reduce or reverse organ injury need to be tested for their effects on morbidity, mortality and patient-centred outcomes. The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) convened a multidisciplinary group of experts to discuss existing knowledge and emerging evidence regarding organ injury in AHF and its associated pathophysiology, clinical assessment, management and research needs.

Pathophysiological mechanisms of organ injury in acute heart failure

Acute heart failure is a heterogeneous syndrome. Patients with *de novo* AHF may have fluid overload less often, whereas those with worsening chronic heart failure (CHF) more commonly have fluid excess. The ESC heart failure guidelines classify patients based on the presence of congestion and/or hypoperfusion.[1] The ‘wet and warm’ (congestion without hypoperfusion) presentation is most commonly encountered (in more than 90% of cases)[1] and is the focus of this manuscript.

Haemodynamic mechanisms of organ injury

Congestion caused by elevated filling pressure

In AHF, blood remains upstream of the ventricles, which results in increased filling pressures (i.e. congestion) that impair organ function. Pulmonary congestion and pulmonary oedema occur when blood remains upstream of the left ventricle because of elevated left atrial pressure, whereas congestion of organs in the abdominal cavity ensues when blood remains upstream of the right ventricle (Figure 1).[7–9] Pulmonary and organ congestion may occur separately or simultaneously. In addition, increased intra-abdominal pressure as a

result of organ congestion and/or ascites may further contribute to injury or impairment of the end-organs impacted by these increased pressures.

Congestion indicates excessive vascular filling of the central venous system. Filling pressure depends on venous compliance and capacitance,[10] plasma volume and cardiac function. Indeed, the transition from CHF to AHF is often attributed to increased sodium avidity and extracellular volume overload, leading to a progressive increase in cardiac filling pressures.[11–13] However, filling pressure is a poor surrogate for volume overload. In one study, 54% of patients hospitalized for AHF gained ≤0.9 kg during the 30 days prior to admission,[14] suggesting that volume overload incompletely characterizes the pathophysiology of AHF. Additionally, weight loss during hospitalization is not necessarily always associated with improved in-hospital or post-discharge morbidity or mortality.[15]

Consequently, it has been suggested that redistribution (from venous capacitance beds to the central venous system) rather than absolute volume overload may be a frequent cause of increased cardiac filling pressures.[16–19] The abdominal compartment probably plays an important role in this as the splanchnic venous system contains 25% of total blood volume.[18] It normally pools and releases blood in order to maintain an optimal cardiac preload. Splanchnic arterioles and veins are very sensitive to changes in sympathetic activity.[16] Increased sympathetic output leads to splanchnic arterial and venous constriction and blood redistribution from the splanchnic capacitance vasculature to circulatory volume, which increases venous return and raises cardiac filling pressures.[16,18] Indeed, this capacitance function becomes compromised during states of longstanding venous congestion and/or increased sympathetic activation in AHF.[18,20] Failure of the abdominal compartment buffer systems may ultimately result in a cardio–abdominal–renal syndrome.[17,18,21]

Organ hypoperfusion—Acute heart failure with a clinical profile of low cardiac output and subsequent organ hypoperfusion (cold–dry or cold–wet[1]) is much less common than a profile of congestion with normal perfusion. It is usually associated with low systolic blood pressure (<90 mmHg) and mean arterial pressure (<65 mmHg) (i.e. cardiogenic shock). Incidences of cardiogenic shock are 5.7–10.1% in acute myocardial infarction[22,23] and approximately 4% in AHF.[1,2,24] The aetiology of cardiogenic shock is acute coronary syndrome in 80% of cases.[25]

Perfusion that is inadequate to meet the metabolic demands of tissues results in hypoxia and inadequate aerobic metabolism and, ultimately, cell injury, cell death, tissue injury and organ failure. Patients with low output syndrome have more chronic or subacute manifestations of poor perfusion, whereas cardiogenic shock is characterized by an abrupt onset. Organ impairment in the setting of shock is of prognostic importance. In the CardShock study, confusion, elevated blood lactate and a reduced glomerular filtration rate (GFR) were significant predictors of in-hospital mortality.[25] Of note, excessive diuretic therapy may reduce cardiac preload, thereby diminishing stroke volume and contributing to the shock state iatrogenically.[26]

Neurohormonal response and inflammation in acute heart failure: impacts on endothelial glycocalyx and vascular function

The neurohormonal and inflammatory response to systemic congestion and/or peripheral hypoperfusion, if present, may further contribute to organ injury.[26–28] Neurohormones, oxidative stress and inflammation may also impair the structure and function of the endothelial glycocalyx (eGC) that is composed of glycosaminoglycan (GAG) networks.[29] These GAG networks function as sodium buffers and play important roles in fluid homeostasis and endothelial function. In heart failure, neurohormonal alterations disrupt GAG structure, leading to loss of the interstitial buffer capacity and disproportionate interstitial fluid accumulation.[29] Moreover, a diminished eGC results in increased vascular resistance and disturbed endothelial nitric oxide production, leading to endothelial dysfunction.[29] Endothelial dysfunction increases left and right ventricular systolic workload, potentially contributing to organ injury,[30] and is a predictor of morbidity and mortality in heart failure of any stage.[31–34]

Organ systems impacted by congestion in acute heart failure: progression from injury to failure

Heart

Venous or systemic congestion increases preload, which leads to increased ventricular wall stress, valvular regurgitation, myocardial stretch, remodelling, ventricular myocyte necrosis and a progressive decline in cardiac function.[35] Natriuretic peptides are released from the atria or ventricle under such conditions of wall stretch or cardiac stress.[36]

Cardiac troponin is detectable in a large proportion of patients with AHF, especially with high-sensitivity assays,[37] revealing non-ischaemic myocyte injury or necrosis.[37–39] Troponin release may be secondary to increased wall stress, structural changes in the myocardium, elevated myocardial pressure, direct toxicity of circulating catecholamines or inflammation.[37] In the Relaxin in Acute Heart Failure (RELAX-AHF) study, 90% of patients had high-sensitivity troponin T (TnT) levels above the 99th upper reference limit, with a median value of 0.033 μg/L.[40] Conversely, patients without detectable high-sensitivity cardiac-specific TnT (cTnT) may be at decreased risk for subsequent events.[41]

Lungs

Rises in hydrostatic left atrial pressure and mitral regurgitation are transmitted backward as increased pressure to the pulmonary capillaries, creating an imbalance in capillary Starling forces. These changes increase the regular fluid filtration rate to the interstitium, causing lung stiffness and, in some patients, dyspnoea. The lymphatic system regularly drains interstitial fluid, but when interstitial pressure exceeds pleural pressure and surpasses drainage capacity, fluid moves to pleural and intra-alveolar spaces, causing pleural effusion and alveolar oedema.[42] Individual susceptibility and genetic characteristics, often involving nitric oxide interactions, may explain why some patients develop pulmonary oedema and others with similar haemodynamics do not.[43–45] An inflammation-triggered increase in

permeability of the pulmonary vasculature may play a role in patients who develop pulmonary oedema despite relatively low hydrostatic pressures.[46]

Repetitive or severe decompensations may result in cardiopulmonary remodelling (i.e. endothelial dysfunction, proliferation of myofibroblasts, fibrosis and thickening of the extracellular matrix) with an impairment in alveolar gas diffusion properties,[47] pulmonary vasoconstriction and, finally, pulmonary hypertension.[48] This process also leads to the restrictive ventilation pattern observed in CHF.[49] The bronchial tree is also affected, which may lead to an obstructive or reactive airway disease pattern.[50]

Kidneys

Cardiorenal syndrome refers to the pathophysiological interplay between the heart and kidney. Type 1 cardiorenal syndrome is manifested as an acute cardiac event (e.g. AHF) that results in kidney injury and renal dysfunction.[9] Depending on its definition, the reported incidence of worsening renal function during AHF hospitalization is 20–30%.[51]

Systemic congestion was a stronger predictor of worsening renal function than cardiac output or mean arterial pressure in analyses of patients with decompensated advanced heart failure.[52–54] Recent evidence from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial showed no positive association between cardiac index and renal function,[55] suggesting that worsening renal function cannot be predominantly attributed to reduced cardiac output in the population of patients represented by this analysis (i.e. patients who are hospitalized for decompensated heart failure without shock).[54] Elevated central venous pressure may worsen renal function through several different mechanisms, including pressure-induced reduction in renal blood flow, renal hypoxia, increased interstitial pressure and interstitial fibrosis.[56] Other contributors to acute kidney injury or worsening renal function in AHF include inflammatory mediators (e.g. infection, tissue damage), iatrogenic damage (e.g. contrast media, nephrotoxic medication), low cardiac output[57] and elevated intra-abdominal pressure.[17]

Type 1 cardiorenal syndrome consists of subclinical injury, which can be detected by tubular markers (Table 1), and acute kidney injury, which is reflected by a rise in functional markers (creatinine and cystatin C). Whether tubular markers in plasma or urine will be helpful in distinguishing these two clinically important entities remains unproven. Kidney Disease Improving Global Outcomes (KDIGO) defines acute kidney injury as indicated by any of the following: an increase in serum creatinine by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h; an increase in serum creatinine to ≥1.5 times the baseline level, which is known or presumed to have occurred within the prior 7 days, and urine volume of <0.5 mL/kg/h for 6 h.[58] Impaired baseline renal function is the strongest risk factor for acute kidney injury,[59] suggesting that underlying intrinsic kidney disease is an important determinant of kidney reserve and the renal response to AHF and aggressive diuretic treatment.

The clinical progression of renal dysfunction in patients with AHF is complex and may follow any of several pathways. In some patients, clinical improvement of the AHF state leads to improved renal function. Prior studies have found a small absolute increase in serum

creatinine (i.e. 0.3 mg/dL) within 48 h, as well as a cystatin C increase of 0.3 mg/L, to be clinically important markers of acute kidney injury and to predict death or hospitalization for heart failure in patients with AHF.[4,51,60–63] However, patients who experience transient worsening of renal function in conjunction with clinical heart failure improvement may have 'pseudo worsening renal function' and may not be at increased risk for adverse events.[63,64] Pseudo worsening renal function is mostly the result of changing intraglomerular haemodynamics rather than renal injury. Although aggressive fluid removal is related to deterioration in renal function and haemoconcentration, haemoconcentration is associated with improved survival in AHF.[65] In fact, a recent secondary analysis suggested improved renal function may be associated with worsened outcomes when compared with worsening renal function.[66] Clearly, the clinical scenario (i.e. improved or worse) must be considered when interpreting changes in renal function. Thus, some degree of 'worsening renal function' is acceptable while effective decongestion is ongoing. Finally, only very few patients with cardiac improvement will have renal tubular injury and experience an irreversible decline in GFR that is prognostically important. Unfortunately, it is very difficult to predict the renal response to decongestion.

Liver

Hepatic dysfunction is present in 20–30% of patients with AHF.[7,67–69] Elevated liver enzymes portend a poor prognosis.[7] Hepatic dysfunction is also closely related to renal dysfunction in AHF (i.e. cardio–renal–hepatic syndrome). These conditions may have synergistic prognostic implications.[70–73]

In the setting of venous congestion, cholestasis is observed with elevation of alkaline phosphatase, bilirubin and γ-glutamyltransferase (GGT).[68,74,75] Cholestasis is a more common finding in patients with AHF than the more ominous finding of centrilobular necrosis and elevated transaminases as a result of hypoperfusion in the setting of hypoxic hepatitis.[74] Hypoxic liver injury is the most common cause of massively raised aminotransferase levels in hospital.[76] It occurs in 5–10% of patients with critical illness[77] and is a strong risk factor for mortality in the intensive care unit (ICU).[78]

Intestine

Intestinal morphology, permeability and absorption are altered in heart failure.[79–81] Increased intestinal permeability and an augmented bacterial biolayer may contribute to the origins of both chronic inflammation and malnutrition.[80,81] Systemic/venous congestion, sympathetic vasoconstriction and low cardiac output contribute to decreased flow in the splanchnic microcirculation and increase the risk for bowel ischaemia.[18] Ischaemia causes epithelial cell dysfunction and loss of the barrier function of the intestine, which allows lipopolysaccharide or endotoxin produced by gram-negative gut bacteria to enter the circulatory system.[18] These effects trigger systemic inflammation and cytokine generation, leading to several abnormalities of cardiomyocyte function and energetics.[18] Interestingly, the Mini Nutritional Assessment revealed that 75% of patients with AHF had malnutrition or were at risk for malnutrition, suggesting this pathophysiology is highly prevalent.[82]

Brain

Normal cerebral perfusion is generally very stable: there is a short time window before cerebral damage occurs in the setting of hypoperfusion. Impairment of higher cortical function can occur in at least three inseparable phenotypes in patients with AHF: depression, cognitive dysfunction, and delirium.[83] Prevalences of cognitive impairment in AHF of 54–75% have been reported.[84–87] Delirium is an acute disorder of inattention and global cognitive dysfunction, and is associated with significant adverse outcomes in patients with acute medical illness.[88] Cerebral dysfunction is associated with an independent increase in mortality in patients with AHF.[89,90]

Hypoxaemia is the primary cause of cerebral dysfunction in AHF, but other factors (e.g. inflammation, stress and neurohormonal dysregulation) may also play significant roles.[91] As well as higher cortical dysfunction, impaired neurocardiac reflexes may affect haemodynamic control of the vasculature and myocardial performance, based on feedback from peripheral tissues to the brain. Diversion of the chemoreflex sensitivity occurs in the setting of altered haemodynamics (e.g. congestion) and may worsen with increasing severity of heart failure.[92,93] Silent cerebral infarctions, hypotension, disturbances of cerebral metabolism, cardiac embolism, frailty and low adherence to medications may also contribute to cognitive dysfunction and depression in AHF.[89]

Clinical and biochemical assessments of acute heart failure and organ injury

Initial work-up

Patients presenting to the emergency department (ED) with symptoms of AHF require an extensive work-up to differentiate between AHF and other causes of dyspnoea, monitor response to therapy, quantify risk, and determine the need for admission. Rapid and accurate diagnosis may facilitate faster initiation of decongestive and other therapies, which, in turn, may reduce or prevent the extent of organ injury, but this hypothesis needs to be tested. Importantly, diagnostic and therapeutic plans commonly occur in parallel in patients suspected of AHF.

Diagnosing and monitoring pulmonary oedema

Pulmonary oedema is characterized by pulmonary congestion in the face of an acutely increased preload or afterload, with a rapid onset, extensive alveolar flooding and significant respiratory distress. An abrupt increase in pulmonary congestion leads directly to decreased pulmonary compliance, which further contributes to tachycardia, tachypnoea and hypoxaemia. Acute pulmonary oedema is characterized by increased work of breathing with a respiratory rate of >25 breaths/min and peripheral oxygen saturation by pulse oximetry (SpO_2) of <90%.94 Monitoring of SpO_2 provides reliable information about arterial oxygen saturation (SaO_2).95 Respiratory rate96 and $SpO_2$97 also closely correlate with AHF severity and mortality. Increases in peripheral oedema and body weight occur in a relatively small proportion of pulmonary oedema patients, suggesting that relative volume

redistribution, as opposed to an absolute increase in total body fluid, may play a major role in the pathophysiology of the pulmonary oedema phenotype.[19]

Blood gas analysis of venous samples can be useful for a rapid assessment of acid–base status.[95] Arterial blood gas analysis is indicated in patients with suspected severe hypoxaemia, hypoventilation and cardiogenic shock, high risk or suspicion of hypercapnia, or in whom oxygenation cannot be assessed reliably by pulse oximetry.[94] Dyspnoea causes hyperventilation and consequent hypocapnia,[98] especially in mild or early stages of pulmonary oedema. A significant fall in alveolar ventilation occurs in patients with concomitant chronic obstructive pulmonary disease (COPD) and in those with severe or advanced acute pulmonary oedema and respiratory fatigue, which usually will lead to hypercapnia. Mixed acidosis (respiratory and metabolic) is the predominant blood gas alteration in severe acute pulmonary oedema.[99–101] Severe metabolic acidosis, seen in cardiogenic shock, triggers hyperventilation (Kussmaul breathing) and contributes to respiratory distress.[98] Blood lactate reflects the severity of hypoperfusion and shock.

It is estimated that 20–35% of patients have concomitant COPD and heart failure,[102] and differentiating between the two conditions can be difficult because of overlapping symptoms and physical examination findings. Natriuretic peptides can be elevated in COPD as a result of the effects of COPD on the right ventricle.[103,104] However, orthopnoea and paroxysmal nocturnal dyspnoea are usually more characteristic of heart failure, and elevations of natriuretic peptides are usually more modest than those occurring in the setting of AHF.[105] Pulmonary function testing should be postponed until patients are stable and decongested because congestion may cause an obstructive pattern.[103] Pulmonary congestion attributable to AHF can also be misdiagnosed as multifocal pneumonia.[2] Clinical assessment (fever, leukocyte count, sputum, cultures) and imaging with ultrasonography or chest radiography are necessary to obtain a definitive diagnosis. In the ICU setting, pulmonary artery or transpulmonary thermodilution (PiCCO) catheters may provide important information regarding cardiac output, capillary wedge pressure and extravascular lung water (EVLW).[46] They may be helpful in selected haemodynamically unstable patients in whom the mechanism of deterioration is unknown.[1]

Imaging

Chest X-ray—Chest X-ray is widely available and remains a standard component of the AHF evaluation. It can detect pulmonary venous congestion, pleural effusion, interstitial or alveolar oedema, and cardiomegaly, but chest X-ray findings may be normal in up to 20% of patients.[1,94,106]

Echocardiography—In acute situations, focused transthoracic echocardiography is typically performed and interpreted by clinicians at the bedside, and portable or pocket ultrasound systems can provide similar levels of accuracy.[107]

Comprehensive echocardiography provides detailed information about cardiac structure and function.[108,109] Inferior vena cava diameter may be increased and its respiratory variation suppressed in patients with AHF, findings that support its diagnosis.[110] Echocardiography can also provide an estimate of left atrial pressure with mitral valve inflow and left

ventricular tissue Doppler assessments (E/e′ ratio). Sonographic assessment includes examination of the lungs and pleural space for detection of pulmonary oedema and pleural effusions.[111,112] Echocardiography is preferred within 48 h of admission in patients with *de novo* AHF or unknown cardiac function.[1] Immediate echocardiography is necessary in haemodynamically unstable patients or suspected acute life-threatening structural or functional cardiac abnormalities.[1]

Lung ultrasound—In dyspnoeic patients presenting to the ED, lung ultrasound is more accurate than auscultation or chest X-ray for the detection of pulmonary congestion in AHF.[113–116] Lung ultrasound can be performed within 2–5 min using either standard ultrasound equipment or pocket devices[111,117] with investigation of three or four zones for B-lines on each hemithorax and the presence of pleural effusions laterally.[112,114] Vertical B-lines provide a graded measure of EVLW (interstitial or alveolar oedema) with high inter-rater reproducibility after a short duration (i.e. 30 min) of training.[114,118] At least three B-lines in two or more intercostal spaces bilaterally are considered indicative of interstitial or alveolar oedema in the acute care setting.[111,112,114,117,119] Despite their high accuracy in the identification of pulmonary oedema in patients with suspected AHF, B-lines can also be found in other conditions, such as interstitial lung disease, acute respiratory distress syndrome, pulmonary contusions and pneumonitis.[112]

Serial assessment with lung ultrasound may be useful for monitoring treatment effects in patients with AHF.[119–121] Importantly, hospitalized patients with residual pulmonary congestion at discharge are at risk for subsequent heart failure hospitalizations or death.[119,122–124]

Biomarkers

Blood and urine biomarkers quantify biochemical signatures that are closely related to organ injury and functional impairment. Well-validated and inexpensive biomarkers are available to quantify injury or impairment of the heart, kidneys or liver and can be used routinely (e.g. natriuretic peptides, cardiac troponin, serum creatinine, cystatin C, albuminuria, blood urea nitrogen, transaminases, coagulation factors, alkaline phosphatase, bilirubin).[4] Other emerging biomarkers are currently under study (as noted below) and may have future roles.

Natriuretic peptides are recommended for measurement in all patients with acute dyspnoea and suspected AHF.[1] Acute heart failure is unlikely in patients with BNP of <100 pg/mL, NT-proBNP of <300 pg/mL or MR-proANP of <120 pg/mL.[1] Elevated natri-uretic peptide levels may be attributable to other cardiac or non-cardiac causes; results must therefore be interpreted in the clinical context.[1,125] Further, obesity may lead to falsely low natriuretic peptide levels, and this should be considered when diagnosing or excluding AHF in this cohort.[126] Procalcitonin levels may aid in the differential diagnosis of pneumonia in patients with AHF and suspected concomitant infection.[127,128] Other biomarkers (e.g. soluble ST2, galectin-3, GDF-15) may have clinical roles in the future, primarily in prognosis and risk stratification.[129]

Cardiac injury is detected by high-sensitivity cardiac troponin I or T assays. Although patients with AHF and elevated troponin are at higher risk than those with undetectable

troponin,[94] it is unclear whether any inpatient interventions impact the trajectory of their risk profile (in the absence of acute myocardial infarction).

Kidney injury can be detected and quantified using a combination of urine output and blood biomarkers of renal function (e.g. cystatin C, serum creatinine to calculate estimated GFR, albuminuria, blood urea nitrogen[63]), or blood and/or urine markers of tubular injury [e.g. neutrophil gelatinase-associated lipocalin (NGAL), pen-enkephalin and KIM-1, although these may not be widely available in clinical practice]. Functional biomarkers have low sensitivity and high specificity, whereas tubular injury markers have high sensitivity and low specificity to detect kidney injury. Several of these markers are elevated in heart failure, both acute and chronic, and are associated with worse survival.[130,131] However, their ability to predict acute kidney injury has been disappointing, limiting their clinical utility. In AHF, levels of urinary NGAL did not differ between patients with and without worsening renal function,[132] and the Acute Kidney Injury Neutrophil Gelatinase-Associated Lipocalin Evaluation of Symptomatic Heart Failure Study (AKINE-SIS) showed that plasma NGAL was not superior to creatinine in predicting worsening renal function in patients with AHF.[133] These data emphasize that progression from tubular damage to reduced function is incompletely understood.

An acute rise in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels signals liver cell necrosis. Coagulation factors reflect actual hepatic synthetic function, especially in acute organ failure, whereas albumin, which has a half-life of 2–3 weeks, represents hepatic synthetic capacity in chronic stable conditions. Alkaline phosphatase, GGT and, to a lesser extent, bilirubin are cholestasis markers. Arterial ammonia may serve as a surrogate marker of hepatic encephalopathy.[134,135]

Circulating trimethylamine N-oxide (TMAO), a gut-derived metabolite, is associated with AHF and is predictive of death or rehospitalization. Transthyretin (prealbumin) provides prognostic information in combination with the Mini-Nutritional Assessment in patients with AHF.[82]

Research is ongoing to determine the clinical roles of vascular and endothelial biomarkers such as mid-regional pro-adrenomedulin,[136] pro-endothelin-1 and endothelin-1.[137] Recently, circulating CD146 appeared to indicate the level of congestion in AHF.[138]

Clinical management tools in acute heart failure

Supplementary oxygen, non-invasive and invasive ventilation

Patients with AHF should be immediately assessed for respiratory distress in the pre-hospital or ED setting.[94] Patients with mild acute respiratory failure present with hypoxaemia and/or other mild blood gas abnormalities without signs of respiratory distress and account for nearly 30% of the AHF population.[98,139] Oxygen therapy is recommended in these patients.[94,140] Recently, conservative oxygen therapy (SpO_2 targets: 94–98%) proved to be safer than conventional oxygen therapy (SpO_2 targets: 97– 100%) in medical ICU patients.[141] In acute pulmonary oedema, non-invasive ventilation is superior to conventional oxygen therapy.[142,143] Continuous positive airway pressure (CPAP) does not

require specialized training and may be administered without a ventilator, which is an advantage in the pre-hospital or ED setting. Meta-analyses have shown evidence that it reduces respiratory distress, endotracheal intubation and even mortality in high-risk patients.[142–144]

Non-invasive pressure support ventilation applied with positive end expiratory pressure (PEEP) provides inspiratory support and is appropriate in patients with hypercapnia. Expertise and appropriate equipment are necessary to synchronize the patient's inspiratory efforts and the ventilator. Non-invasive pressure support ventilation reduces respiratory distress and the need for endotracheal intubation, but data on its impact on mortality and its superiority in comparison with CPAP are inconclusive.[145,146] Severe respiratory distress and impending exhaustion may be indications for endotracheal intubation and invasive mechanical ventilation.[94]

In addition to the use of supplementary oxygen and ventilatory support, other means of alleviating dyspnoea and ventilation disorders may be indicated. These include the removal of clinically significant amounts of pleural fluid and administration of inhaled bronchodilators (in COPD and asthma). Opioids have been widely used in this setting, but there are conflicting data on their safety and efficacy.[147]

Pharmacological approaches to treating congestion and preventing organ injury

The therapeutic approach to congestion depends on whether vascular-type fluid redistribution or cardiac-type fluid accumulation[1] is the primary cause of the elevated cardiac filling pressures[148,149] (Figure 2). More than 80% of patients are initially treated homogeneously with i.v. diuretics without consideration of the underlying pathophysiology.[11,150]

Diuretics—Diuretics are guideline-recommended first-line therapy in 'wet and warm' patients in whom congestion is predominantly attributable to fluid accumulation and volume overload.[1] Diuretics are generally ineffective in patients with congestion caused by vascular-type fluid redistribution,[1] generally observed as increased congestion despite a lack of weight gain and predominantly indicated by hypertension. Loop diuretics should be prescribed i.v. at a dose sufficient to achieve meaningful natriuresis, usually 20–40 mg of i.v. furosemide (or equivalent: torasemide 5–10 mg, bumetanide 0.5–1.0 mg[1]) in new-onset AHF or at least the oral dose in patients with CHF.[1,151] Bowel oedema impairs gastrointestinal absorption; therefore, parenteral administration is preferred. Strategies to address inadequate diuresis include the administration of a continuous infusion as an alternative route of administration (e.g. 1–10 mg/h of furosemide or equivalent, depending on the current dose) or additional loop diuretic boluses; these strategies resulted in similar degrees of symptomatic relief and did not differ in terms of adverse effects in the Diuretic Optimization Strategies Evaluation (DOSE) trial.[151] Patients respond individually to different strategies and it is reasonable for physicians to tailor the choice of strategy to the specific patient. Combination drug therapy targeting different segments of the nephron [e.g. thiazide (hydrochlorothiazide) and thiazide-like (metolazone),[152] diuretics, mineralocorticoid receptor antagonists or acetazolamide] may be helpful in some patients

with an inadequate natriuretic response to loop diuretics,[149,153] although strong evidence is lacking.[1] A prospective trial with acetazolamide is currently being planned. Diuretics alleviate congestion by decreasing cardiac filling pressure without increasing ventricular contractility or cardiac output. High diuretic doses may decrease renal blood flow and GFR by activating the renin–angiotensin–aldosterone system (RAAS) and/or sympathetic nervous system,[154–156] although recent studies in patients on guideline-directed therapy question whether the RAAS is activated to a significant extent.[157] Tubuloglomerular feedback may also play a role,[158] whereby increased sodium chloride reabsorption by the macula densa results in adenosine release and increased renin activity, leading to afferent arteriole vasoconstriction and a decrease in single nephron GFR.[159,160]

Vasodilators—Vasodilators may be used as first-line therapy to unload the heart and increase venous capacitance in patients with AHF and hypertensive, vascular-type fluid redistribution.[1,57,149] Vasodilators improve ventricular function by reducing afterload and decrease symptoms by reducing cardiac filling pressure.[1] Nitrates (e.g. nitroglycerin, nitroprusside) are direct-acting vasodilators and are used most frequently. They have not been evaluated in adequately powered studies specifically targeting the ‘wet and warm’ phenotype; thus, they have not been shown to improve clinical outcomes.[161] Care should be taken to avoid hypotension.

Serelaxin was studied in the Relaxin in Acute Heart Failure (RELAX-AHF) trial and was found to improve dyspnoea in comparison with the placebo plus standard of care arm.[162] As recently presented during the HFA 2017 Congress, RELAX-AHF-2, a phase 3 study, was neutral regarding the co-primary endpoints, and publication of the results will be forthcoming.

Ularitide was studied in the Trial of Ularitide’s Efficacy and Safety in Patients with Acute Heart Failure (TRUE-AHF).[163] At 48 h, ularitide decreased NT-proBNP and systolic blood pressure to a greater extent than placebo, and other evidence of intravascular decongestion was observed (significant increases in haemoglobin and serum creatinine and decreases in hepatic transaminases compared with placebo). No difference between groups was observed in the co-primary endpoints of clinical composite score at 48 h or cardiovascular mortality over a median follow-up of 15 months.[163]

Vasopressors, inotropes and inodilators—Inotropes (e.g. dobutamine), inodilators (e.g. levosimendan, milrinone) and vasopressors (norepinephrine is preferred over dopamine based on a subgroup analysis that suggested fewer side effects and lower mortality with norepinephrine, as noted in heart failure guidelines[1,164]) should only be used when cardiac output is severely reduced, vital organ perfusion is compromised, filling pressures are normal or high, and patients cannot be stabilized by other means[1,94] because of their associations with increased mortality.[165,166] Recent evidence suggests that epinephrine should be avoided in cardiogenic shock.[167]

Organ-specific management options

Heart—Current guidelines for heart failure suggest the use of short-term mechanical circulatory support should be considered in patients who remain unstable with insufficient

end-organ perfusion despite medical therapy.[1] An intra-aortic balloon pump is not routinely recommended in cardiogenic shock.[94] A device selection strategy [i.e. extracorporeal membrane oxygenation (ECMO), extracorporeal life support (ECLS), left ventricular assist device (LVAD)] based on severity [i.e. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) criteria] is outlined in the ESC heart failure guidelines.[1]

Kidney—Treatment of venous congestion may prevent or minimize kidney injury in AHF.[52–54] The therapeutic goal is to achieve the lowest venous filling pressures without deteriorating cardiac output. Ultrafiltation may be considered in patients in whom decongestion goals are not met with vasodilators or loop diuretics.[1] Data are inconclusive for the effectiveness of ultrafiltration compared with diuretics alone.[168–170] Inotropes may be considered in patients with deteriorating cardiac output and renal perfusion in the setting of decongestion. Nephrotoxic agents and procedures should be avoided during the AHF presentation.

Liver—Liver-specific management involves appropriate supportive treatment for the problems induced by liver impairment or failure (e.g. coagulopathy, hypoglycaemia, hypoalbuminaemia, hepatopulmonary syndrome),[171–176] but these are not specific to patients with AHF. Liver impairment can impact the pharmacokinetics of some drugs commonly used in heart failure, potentially leading to adverse effects or toxicity caused by elevated serum concentrations of some drugs (e.g. warfarin).

Intestine—Few interventions target gut protection in the setting of AHF.[79] In addition to loop diuretics and vasodilators, paracentesis in patients with ascites and elevated intra-abdominal pressure (>8 mmHg), or ultrafiltration may be strategies to consider in specific patients.[21,177–179]

Gaps in knowledge and future directions

Defining adequate endpoints of decongestion is a major clinical challenge of managing patients with AHF. Change in body weight is often used as a guide, but this approach is frequently inadequate as body weight is not increased in all patients and does not reflect congestion caused by vascular-type fluid redistribution. Evidence-based clinical and biochemical indicators of adequate decongestion are lacking; thus, vasodilator or diuretic dose adjustments are largely empirical. Developing reliable criteria and accurate methods for assessing the extent of congestion and determining optimal decongestion are crucial unmet needs because persistent congestion is a marker of worse prognosis after discharge.[180] Point-of-care imaging may have potential, primarily for the evaluation of pulmonary congestion. Novel, effective and safe pharmacological or mechanical methods to achieve decongestion are needed. The patterns of congestion in AHF with preserved ejection fraction are not well characterized and warrant investigation, although the available evidence suggests that patients with heart failure from reduced or preserved ejection fraction have similar characteristics of congestion at presentation (e.g. oedema, orthopnoea, elevated jugular venous pressure, dyspnoea on exertion).[181]

Organ-specific injury markers suitable for clinical practice are lacking for many organs (e.g. brain, lung, intestine, endothelium, vasculature). Injury markers for these organs would be valuable, along with evidence-based recommendations for monitoring, leading to possible intervention strategies. Even where organ-specific injury markers exist (e.g. cardiac troponin, markers of renal or hepatic injury), research is needed to guide their interpretation. The clinical progression of organ injury to dysfunction and ultimately failure is not well characterized and the extent to which injury and dysfunction are reversible or irreversible in the setting of AHF is not known. The clinical importance of low levels of detectable troponin is not well understood and whether or not treatments that target troponins alter risk is unknown. The same is true for novel prognostic markers such as mid-region adrenomedullin and soluble ST2. It remains uncertain whether decongestion targeting reduction in traditional markers of heart failure (i.e. natriuretic peptides) is more beneficial than clinical guidance.[182] More research is needed to establish the appropriate pathway (i.e. discharge or further evaluation) in otherwise stable patients with persistently elevated biomarkers.

The treatment of pulmonary oedema remains largely opinion-based as there is a general lack of robust evidence to guide therapy. Similarly, although small studies suggest that vasodilators are preferable as first-line therapy in AHF patients with hypertension, a definitive trial testing this strategy is required to fill this evidence void. Furthermore, no therapy has shown simultaneous benefits in symptomatic relief, haemodynamic improvement, increased survival and end-organ protection.[183] New methods such as thoracic impedance monitoring have been used to detect pulmonary oedema in the research setting.[184]

The concept that treatment of congestion can reduce or prevent organ injury needs to be tested in randomized trials, and the effects of preventing organ injury on morbidity, survival and health economics require validation. Whether regulators will accept prevention of organ injury as an endpoint in AHF trials remains to be determined; adequate reassurance of safety (i.e. in terms of mortality) would also need to be demonstrated. Engagement with payers is needed to determine their attitudes towards such an endpoint. It is reasonable to consider that payers may be supportive of therapies that prevent organ injury if their use leads to shorter ICU or overall hospital stays, decreases short-term readmissions or reduces the need for other interventions (e.g. haemodialysis, mechanical circulatory support), but this evidence must be generated.

Conclusions

Managing patients with AHF remains a clinical challenge and current therapies have uncertain impacts on long-term morbidity and mortality. The use of therapies that prevent or reverse congestion-induced organ injury may represent a strategy to reduce subsequent organ impairment and morbidity that is more successful than the traditional approach of targeting dyspnoea relief. Although much has been learned about the role of congestion in promoting organ injury, future research efforts should focus on defining the specific pathophysiological mechanisms through which congestion leads to organ injury, determine whether

decongestive therapies can prevent or reverse organ impairment, and evaluate the impact of an organ-preserving strategy on long-term clinical outcomes.

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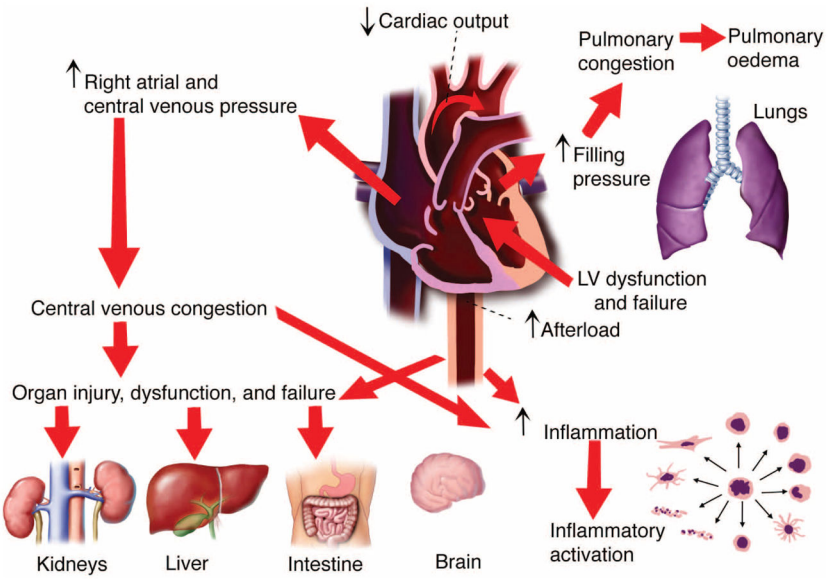

Figure 1.
Relationships between congestion and end-organs. LV, left ventricle.

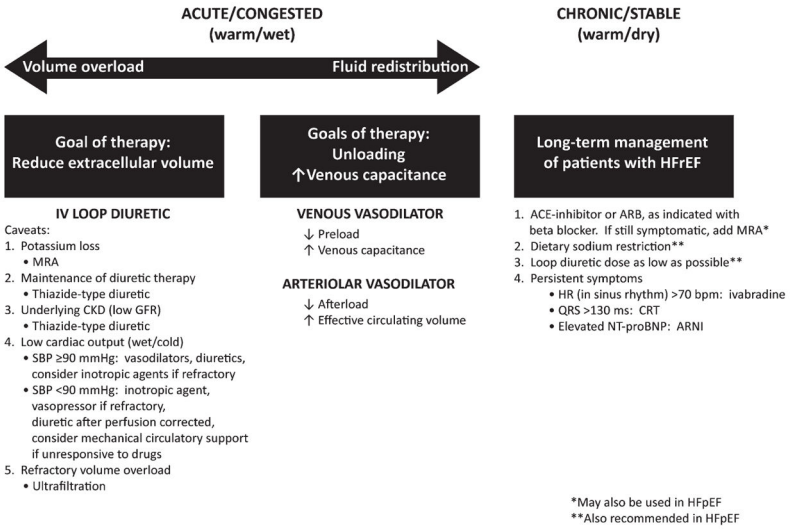

Figure 2.

The pharmacological management of congestion in heart failure. Patients without congestion (i.e. normal filling pressures and no volume overload) should be managed with neurohumoral blockers, the lowest possible dose of loop diuretics, and selected therapies in cases of persistent symptoms. In congestion, it is pivotal to distinguish between the phenotype of volume overload: cardiac-type fluid accumulation (i.e. oedema, ascites, pleural effusion) or vascular-type fluid redistribution. In volume overload, the goal is to remove extracellular fluid through the use of loop diuretic therapy, which should be adequately dosed and administered i.v. Loop diuretics should often be used in combination with diuretic agents acting in other segments of the nephron. Vasodilators may be added cautiously in low cardiac output and systolic blood pressure of >90 mmHg, while avoiding a decrease in mean arterial blood pressure to <65 mmHg. Inotropes are to be used only in severe hypoperfusion. The use of ultrafiltration is limited to selected cases of refractory volume overload. In contrast, vasodilating agents (with a considerably lower dose of diuretics) are the preferred pharmacological option in vascular fluid redistribution. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.

Table 1

Assessment of organ injury in acute heart failure

Organ	Clinical signs and symptoms	Biochemical	Imaging	Other monitoring
Heart (congestion)	Third heart sound, elevated jugular venous pressure, hepatojugular reflux, ascites, pleural effusion, swollen legs	Natriuretic peptides (myocardial stretch), cardiac troponin	Echocardiography, ECG, ultrasound of IVC	Heart rate and blood pressure monitoring, central venous catheter, PiCCO catheter (EVLWI)
Heart (cardiogenic shock)	Cold extremities, pallor, mottling, tachycardia, hypotension, oliguria, mental disturbance, confusion	Lactate; central venous oxygen saturation (SvO_2 or $ScvO_2$); metabolic acidosis	Echocardiography, ECG	As above, plus arterial line, cardiac output monitoring[25] (PAC, PiCCO catheter)
Kidney	Oliguria	Serum creatinine, eGFR, cystatin C, sodium, potassium, biochemical urinalysis	Ultrasound	Urinary output
Lung	Dyspnoea, orthopnoea, increased work of breathing, tachypnoea, rales	Peripheral arterial oxygen saturation, arterial and venous blood gases	Chest X-ray, lung ultrasound, computed tomography	PAC, PiCCO catheter, impedance
Liver	Hepatomegaly	Transaminases, alkaline phosphatase, bilirubin, albumin	Ultrasound	
Abdomen	Ascites	N/A	Ultrasound	Intra-abdominal pressure measured by Foley catheter
Gut	Appetite loss, abdominal swelling	N/A	N/A	
Vasculature, endothelium	Jugular vein distension,[a] mottling,[b] delayed capillary refill,[b] peripheral oedema,[a] cold periphery[b]	N/A	Ultrasound of IVC	
Brain	Mental disturbance, confusion	N/A		GCS, CAM-ICU, ICDSC[185]

CAM-ICU, confusion assessment method for the intensive care unit; ECG, electocardiography; eGFR, estimated glomerular filtration rate; EVLWI, extravascular lung water index; GCS, Glasgow Coma Scale; ICDSC, Intensive Care

Delirium Screening Checklist; IVC, inferior vena cava; N/A, not applicable; PAC, pulmonary artery catheter; PiCCO, transpulmonary thermodilution [Pulse Contour Cardiac Output]; $ScvO_2$, central venous oxygen saturation; SvO_2, venous oxygen saturation.

[a] Signs of congestion.

[b] Signs of hypoperfusion.