



Congestion in Acute Heart Failure Syndromes: An Essential Target of Evaluation and Treatment

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ABSTRACT

Patients with acute heart failure syndromes (AHFS) typically present with signs and symptoms of systemic and pulmonary congestion at admission. However, elevated left ventricular (LV) filling pressures (hemodynamic congestion) may be present days or weeks before systemic and pulmonary congestion develop, resulting in hospital admission. This “hemodynamic congestion,” with or without clinical congestion, may have deleterious effects including subendocardial ischemia, alterations in LV geometry resulting in secondary mitral insufficiency, and impaired cardiac venous drainage from coronary veins resulting in diastolic dysfunction. It is possible that these hemodynamic abnormalities in addition to neurohormonal activation may contribute to LV remodeling and heart failure progression. Approximately 50% of patients admitted for AHFS are discharged with persistent symptoms and/or minimal or no weight loss in spite of the fact that the main reason for admission was clinical congestion. Accordingly, the assessment and management of pulmonary and systemic congestion in these patients require reevaluation. © 2006 Elsevier Inc. All rights reserved.

KEYWORDS: Acute heart failure syndromes; Outcomes; Pulmonary congestion; Treatment

Acute heart failure syndromes (AHFS) can be defined as rapid or gradual changes in signs and symptoms of heart failure (HF) that necessitate hospitalization and/or an urgent augmentation of existing therapy.^{1,2} Although many lifesaving pharmacologic, nonpharmacologic, and surgical treatments for AHFS are available or under development,^{1,2} these patients continue to experience a poor quality of life and frequent hospitalizations that commonly result from episodes of worsening congestion.^{3,4} Nevertheless, congestion often remains unrecognized and is not appropriately treated in a timely manner before or during hospitalization. This may be responsible, in part, for pathologic processes that lead to a progression of HF and a worsening prognosis. It therefore is critical that clinicians understand the importance of systemic and pulmonary congestion as a target of diagnostic evaluation and therapeutic interventions in AHFS.

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EPIDEMIOLOGY OF ACUTE HEART FAILURE SYNDROMES

AHFS is the direct cause of approximately 1 million hospitalizations and a contributing factor in an additional 2.4 million hospitalizations each year in the United States.⁵ Hospitalizations with a primary discharge diagnosis of HF, largely due to episodes of AHFS, are increasing in both the United States and Europe. Hospital discharges due to HF rose from 399,000 in 1979 to 1,093,000 in 2003, an increase of 174%.⁶ Patients admitted for AHFS are hospitalized for 5.4 days on average,⁵ and this hospital care accounts for nearly 60% of the annual total direct costs of HF.⁶ When both primary and secondary hospital discharge diagnoses are considered, the number of annual hospitalizations due to HF approaches 3 million.^{6,7}

Although in-hospital mortality rates are only in the range of 3% to 4%, the 60- to 90-day postdischarge mortality rate increases to approximately 10%, and the readmission rates during this period approach 25%.^{2,8–11} Recurrent hospitalizations are an important source of costs, accounting for >75% of the \$46 billion in annual HF expenditures.¹²

Table 1 Typical characteristics of patients with acute heart failure syndromes

	EURO HF ⁸	ADHERE ¹³	OPTIMIZE-HF ¹⁴
Patients (n)	11,327	163,447	34,059
Demographics			
Age (yr)			
Mean	71	—	73
Median	—	75	—
Sex (%)			
Women	47	52	52
Men	53	48	48
Race/ethnicity (%)			
Caucasian	NA	72	75
African American	NA	20	18
Place of admission (%)			
General floor	50	11	NA
Cardiology floor/telemetry unit	43	65	NA
Intensive/coronary care unit	NA	13	NA
Medical history (%)			
Prior HF	56	76	87
New-onset HF	27	24	13
Coronary artery disease	68	57	50
Myocardial infarction	39	30	23
Hypertension	53	73	71
Diabetes mellitus	27	44	42
Atrial fibrillation	43	31	31
Pacemaker/ICD	9	21	17
Clinical status (%)			
Any dyspnea	NA	89	90
Dyspnea at rest	40	34	45
Fatigue	NA	31	23
Rales	NA	67	65
Peripheral edema	23	66	65
Cardiogenic shock	<1	2	<1
LVEF <0.40	46	47	52
Outcomes			
>2.5-kg weight loss (%)	NA	49	50
HF symptoms (%)			
Unchanged/worse	NA	<1	<3
Improved but still symptomatic	NA	39	40
Asymptomatic	NA	50	51
Length of stay (days)			
Mean	11		NA
Median		4.3	NA
In-hospital mortality (%)	7	3.9	4
Mortality at 2–3 mo (%)	13.5	NA	9
Readmission at 2–3 mo (%)	24	NA	31

ADHERE = Acute Decompensated Heart Failure National Registry; EURO HF = EuroHeart Failure survey program; HF = heart failure; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NA = not available/not applicable; OPTIMIZE-HF = Organized Program to Initiate Life-Saving Treatment in Hospitalized Patients with Heart Failure.

CLINICAL PRESENTATION OF ACUTE HEART FAILURE SYNDROMES: THE ROLE OF CONGESTION

AHFS has traditionally been considered a problem of volume overload as a result of increased ventricular filling pressure and neurohormonal activation, and/or low cardiac output. Recent data from the Acute Decompensated Heart Failure Registry (ADHERE), Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF), and the EuroHeart Failure survey have shown that most AHFS hospitalizations are caused

primarily by volume overload, rather than by low cardiac output (**Table 1**).^{8,13,14} ADHERE represents the single largest, retrospective data currently available on the presentation and management of AHFS.¹³ Although new-onset HF was responsible for 24% of these hospitalizations, most (76%) were the result of an exacerbation of previously diagnosed HF (**Table 1**).¹³ In these patients, the most common presenting signs and symptoms were dyspnea (89%), rales (67%), and peripheral edema (66%). Moreover, hypertension was significantly more prevalent than was cardiogenic shock. A systolic blood pressure measurement

Table 2 Clinical presentations of acute heart failure syndromes (AHFS)

Clinical Presentation	Incidence*	Signs and Symptoms	Characteristics
Elevated systolic BP	>50%	Usually develop abruptly	Predominantly pulmonary (radiographic/clinical) rather than systemic congestion owing to rapid fluid redistribution from systemic to pulmonary circulation; may have preserved left ventricular ejection fraction
Normal systolic BP	>40%	Develop gradually (days or weeks) and are associated with significant systemic congestion	Despite high ventricular filling pressure, radiographic pulmonary congestion may be minimal because of pulmonary vasculature/lymphatics adaptation due to chronic elevated left atrial pressures
Low systolic BP (<90 mm Hg)	<8%	Usually a low cardiac output with signs of organ hypoperfusion	Many of those patients have advanced or end-stage HF
Cardiogenic shock	<1%	Rapid onset	Primarily complication of acute myocardial infarction, fulminant myocarditis
Pulmonary edema	<3% [†]	Rapid or gradual onset	Clinical: severe dyspnea, tachypnea, tachycardia, and hypoxemia, requiring immediate airway intervention Radiographic: present in ≤80% of patients; often not associated with clinical pulmonary edema
“Flash” pulmonary edema	?	Abrupt onset	Precipitated by severe systemic hypertension; uncorrected, respiratory failure and death ensue. Patients are easily treated with vasodilators and diuretics. After BP normalization and reinstatement of routine medications, patients can be discharged within 24 hr
Isolated right HF	?	Rapid or gradual onset	Not well characterized; there are no epidemiologic data (e.g., acute cor pulmonale, right ventricular infarct)
ACS [‡]	?	Rapid or gradual onset	Many such patients may have signs and symptoms of HF that resolve after initial therapy or resolution of ischemia
Post cardiac surgery HF	?	Rapid or gradual onset	Occurring in patients with or without previous ventricular dysfunction, often related to worsening diastolic function and volume overload immediately after surgery

ACS = acute coronary syndromes; BP = blood pressure; HF = heart failure.

*Of all AHFS.

[†]Its incidence may be related to the definition used (clinical versus radiographic).

[‡]Approximately 25% of patients with ACS have signs/symptoms of HF.

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>140 mm Hg was present in 50% of the patients; in contrast, only 2% had systolic blood pressure <90 mm Hg.¹³ In addition, >50% of patients had preserved left ventricular (LV) function.¹³ OPTIMIZE-HF was designed to improve the treatment of patients with AHFS and accelerate the initiation of HF therapies recommended by evidence-based guidelines.¹⁴ To date, >34,000 AHFS hospitalization records have been entered into this registry.¹⁴ Analyzing these data yields results that are nearly identical to those in the ADHERE analysis (Table 1). Most patients (87%) presented with an exacerbation of previously diagnosed HF, and only 13% had new-onset HF. Similar to ADHERE, the most common presenting signs and symptoms were dyspnea (90%), rales (65%),

and peripheral edema (66%). Fewer than 1% of patients presented with cardiogenic shock; 48% had a systolic blood pressure >140 mm Hg, and 48% had preserved LV function (Table 2).² Accordingly, in the EuroHeart Failure survey, approximately 40% of patients presented with dyspnea at rest, and an additional 35% presented with exertional dyspnea or increasing peripheral edema.⁸ LV function was preserved in >50% of patients, and <1% of patients presented with cardiac arrest or cardiogenic shock.⁸ Also, in the recently published Italian nationwide registry on AHFS, the large majority of patients presented with signs of peripheral and pulmonary congestion confirmed by chest x-ray at the time of admission.¹⁵ Data from the Vasodilatation in the Management of

Acute Congestive Heart Failure (VMAC) trial previously demonstrated that patients admitted with HF had a relatively high pulmonary capillary wedge pressure (PCWP) (25 to 30 mm Hg) and preserved cardiac index (≥ 2.0 to 2.2 L/min per m^2).⁴ Additionally, in a prospective evaluation of 452 patients hospitalized for AHFS, 222 patients (49%) had evidence of congestion with adequate perfusion, compared with only 16 (4%) who had hypoperfusion without evidence of congestion and 91 (20%) with evidence of both congestion and hypoperfusion.¹⁶

Clinical Congestion versus Hemodynamic Congestion

Elevated LV filling pressures are present in a majority of patients presenting with AHFS; however, congestion is often clinically silent in these patients. As mentioned before, congestion often is not recognized until conditions develop that necessitate hospital admission.^{17,18} Given this phenomenon, the elevation of the LV filling pressures that occurs early can be termed “hemodynamic congestion,” as opposed to clinical congestion, which occurs later and is evidenced by dyspnea and orthopnea, pulmonary rales, peripheral edema, and jugular venous distention (JVD) (**Table 3**).¹ The concept of hemodynamic congestion versus clinical congestion describes 2 points on a continuum in the development of congestion but may serve to raise awareness among clinicians that hemodynamic derangements precede clinical manifestation. In a study by Mahdyoon and colleagues,¹⁷ only 7 of 22 patients (32%) with elevated PCWP (≥ 25 mm Hg) had moderate-to-severe pulmonary congestion detected by chest x-ray; 6 patients (27%) had no radiographic evidence of pulmonary congestion. Similarly, rales, edema, and elevated mean jugular venous pressure were absent in 18 of 43 patients with elevated PCWP (≥ 22 mm Hg) in another evaluation.¹⁹ Overall, the combination of clinical signs had only a 58% rate of sensitivity in detecting patients with elevated PCWP.¹⁹

Congestion as the Main Cause of Admission and Readmission for AHFS

Congestion is often not adequately addressed during hospitalization for AHFS, which results in patients being discharged with improved symptoms yet persistently elevated LV filling pressures. This ultimately leads to early readmission when symptoms of congestion recur. In the Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) trial, patients admitted with signs and symptoms of congestion did not experience an adequate resolution of their symptoms. In this study, approximately 60% of patients were discharged with continuing symptoms of dyspnea or fatigue. At 60 days after discharge, approximately 45% of these patients experienced worsening HF, and 25% required rehospitalization.¹⁰ These data generated the hypothesis that persistent high LV filling pressures are not adequately recognized and treated before discharge and that this may be an important cause of subsequent readmissions.

Table 3 Hemodynamic congestion versus clinical congestion

- *Hemodynamic congestion* refers to the state of volume overload resulting in increased left ventricular filling pressure.
- *Clinical congestion* refers to the constellation of signs and symptoms that result from increased left ventricular filling pressure.
- Clinical congestion can be thought to consist of cardiopulmonary congestion (respiratory distress, third heart sound, rales, interstitial/alveolar edema, chest x-ray findings) and systemic congestion (jugular venous distention, peripheral edema).
- Hemodynamic congestion precedes cardiopulmonary congestion by several days.
 - In its preclinical state, hemodynamic congestion can exist without clinical manifestation.
 - Intervention in preclinical hemodynamic congestion may prevent development of clinical congestion that generally requires hospitalization contributing to heart failure progression.
- Resolution of clinical congestion can occur with persistent hemodynamic congestion.

Congestion and Prognosis. Failure to recognize and adequately address congestion seems to increase morbidity and mortality risk. Lucas and colleagues²⁰ studied 146 patients with New York Heart Association (NYHA) class IV HF 4 to 6 weeks after hospital discharge. Patients were divided into 3 groups on the basis of residual symptoms and signs of congestion (orthopnea, JVD, peripheral edema, and weight gain) and need for increased diuretic dose. The 2-year survival rate was 87% in patients with no residual symptoms of congestion, 67% in patients with 1 or 2 residual symptoms of congestion, and 41% in patients with ≥ 3 residual symptoms of congestion. Freedom from congestion, PCWP on therapy, LV dimension, and use of an angiotensin-converting enzyme (ACE) inhibitor were identified as significant univariate predictors of survival.²⁰ Similarly, in a post hoc evaluation of the data from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) trial, severe congestion (defined as the presence of dyspnea, JVD, and peripheral edema) at baseline was associated with an increase in 60-day mortality risk (8.1% vs. 4.9% in patients with and without severe congestion, respectively).¹¹ The Studies of Left Ventricular Dysfunction (SOLVD) reported that congestion (determined by JVD and/or S3 gallop) was associated with a 15% relative increase in the risk of death and 40% relative increase in HF hospitalizations during a 5-year follow-up period.²¹

Additional studies have demonstrated that baseline PCWP may have a prognostic impact in patients with AHFS. A study of patients hospitalized for AHFS reported that a PCWP ≤ 16 mm Hg before hospital discharge was an independent predictor of improved 1-year survival (80.8% vs. 64.1% in patients with persistently elevated LV filling

pressure); in contrast, no survival benefit was reported with improvements in cardiac index.²² The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) also demonstrated that PCWP, and not cardiac output, was one of the most important predictors of 6-month postdischarge survival. Other independent predictors of 6-month mortality were low systolic blood pressure, high blood urea nitrogen, and shorter distance walked on the 6-minute walk test.²³

Pathophysiology of Congestion. Ventricular remodeling, progression of coronary artery disease, valvular abnormalities, renal impairment, and neurohormonal activation play a significant role in the development of clinical congestion in patients with AHFS.¹ Increased LV filling pressures augment LV wall stress, contributing to chamber dilatation and sphericity of the ventricle, which may cause mitral regurgitation, leading to hemodynamic deterioration and ventricular dilation.¹ Increased PCWP can lead to redistribution of excess fluid within the lungs, resulting in interstitial and alveolar edema. However, this redistribution depends on hydrostatic pressure as well as several other factors including the plasma oncotic pressure, permeability and integrity of the alveolar-capillary membrane, and lymphatic drainage.

Elevated filling pressures also increase angiotensin II release and endogenous protease activity that induce tachycardia, vasoconstriction, and fluid retention leading to subendocardial ischemia. Subendocardial ischemia may increase the risk for ventricular arrhythmia and sudden death, and it may contribute to the progression of LV dysfunction and remodeling by myocyte loss through necrosis and apoptosis.¹ In addition, myocardial ischemia from coronary artery disease may be both a cause and a consequence of an acute exacerbation of HF.¹

HF impairs renal perfusion, leading to progressive renal dysfunction.¹ Abnormal renal sodium/water handling leads to fluid retention, increasing the risk for AHFS. Furthermore, this dysfunction diminishes responsiveness to diuretics, complicating the management of this fluid retention. In addition, renal dysfunction causes anemia, leading to further HF progression and hemodynamic deterioration.¹

Patient-related factors such as excessive salt and water intake, nonadherence to medication regimens, and use of cardiac toxins such as alcohol and cocaine may also cause or contribute to congestion. In a sample of 179 consecutive patients hospitalized for AHFS, 42 patients (24%) were noncompliant with drug regimens, 61 (34%) had excessive (≥ 2.5 L/day) fluid intake, and 77 (43%) had excessive dietary sodium intake.²⁴ Calcium channel blockers and most antiarrhythmic agents depress myocardial function.²⁵ Nonsteroidal anti-inflammatory agents promote salt and water retention and interfere with the effectiveness of both loop diuretics and ACE inhibitors.²⁵ Oral hypoglycemic agents, primarily the thiazolidinediones, increase plasma volume,²⁵ β -agonists induce tachyarrhythmia, and over-the-counter

cold medications may contain sympathomimetic agents that increase adverse neurohormonal activation.²⁵

The progressive volume retention produced by these factors can occur gradually and often precedes by several days the development of symptoms and subsequent hospitalization. Adamson and colleagues¹⁸ evaluated the efficacy of using an implantable monitor to continuously assess right ventricular hemodynamics in 32 patients with HF. Twelve of these patients ultimately required admission for AHFS, and 9 of these 12 individuals sustained $>20\%$ increases in right-sided pressures, consistent with volume retention. These hemodynamic changes occurred 4 ± 2 days before the development of symptoms and subsequent hospitalization, with a further increase detected in the 24 hours immediately before hospitalization (**Figure 1**).¹⁸

Evaluation of Congestion. The ability to identify hemodynamic congestion before symptoms arise may help to avoid hospitalizations and reduce disease progression in patients with HF. When compared with hemodynamic measurements, the clinical signs and symptoms of HF demonstrate lower clinical accuracy.^{26,27} Physical examination can provide useful information about hemodynamic congestion in patients with AHFS. In the absence of PCWP measurement, assessments of orthostatic blood pressure changes, the Valsalva maneuver, and/or heart rate and/or blood pressure response to sublingual nitroglycerin may be helpful in identifying patients with high LV filling pressures in the absence of clinical congestion.²⁸

Pulmonary congestion may be manifested on chest x-ray as cardiomegaly, redistribution of pulmonary vessels, increased density of and enlarged hilar vessels, perihilar haze, perivascular and peribronchial cuffs, Kerley lines, and sometimes as alveolar edema.

Several studies have investigated the ability of symptoms, signs, and chest x-ray findings to predict a PCWP >18 to 20 mm Hg.²⁹ Physical findings (orthopnea, edema, rales, third heart sound, and elevated jugular venous pressure) or radiographic signs (cardiomegaly, vascular redistribution, and interstitial and/or alveolar edema) had poor predictive value for identifying patients with PCWP ≥ 30 mm Hg. Radiographic pulmonary congestion was absent in 53% of patients with a PCWP of 16 to 29 mm Hg and in 39% of patients with a PCWP ≥ 30 mm Hg.²⁹ Although chest x-ray can be a useful tool in the evaluation of patients with HF, the absence of chest x-ray findings does not exclude the presence of high PCWP (hemodynamic congestion).²⁹

Surrogate markers such as monitoring for signs and symptoms of congestion and daily weight measurements are used routinely in the outpatient setting to detect the warning signs of AHFS.

Echocardiography is another important tool in the diagnosis of HF. However $\leq 50\%$ of HF patients exhibit normal ejection function by echocardiography, so the usefulness of this tool can be limited in these individuals.³⁰ Nevertheless, echocardiography can be used in these patients to accurately

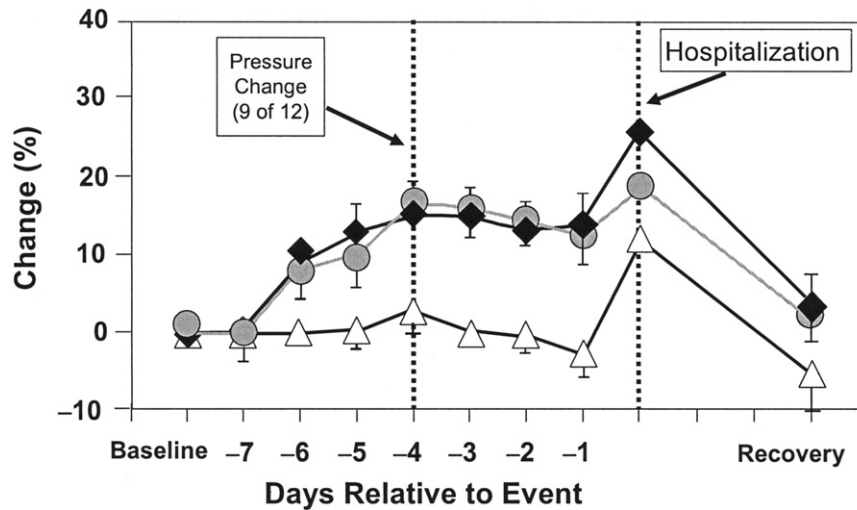


Figure 1 Change from baseline in heart rate (*triangles*), right ventricular systolic pressure (*circles*), and estimated pulmonary artery diastolic pressure (*diamonds*) before and during admission for acute heart failure. In 9 of 12 subjects, significant changes in right ventricular and pulmonary artery pressures were detected 4 ± 2 days before symptomatic decompensation and hospitalization. (Reprinted with permission from *J Am Coll Cardiol.*¹⁸)

assess LV end diastolic diameter, left atrium diameter, and pulmonary artery pressure.³⁰

Other noninvasive inpatient diagnostic tools are also typically used to evaluate congestion. Serum measurements of brain-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) can be used as a surrogate marker of elevated PCWP.^{28,31–35} Although serum concentrations of BNP or NT-proBNP cannot be used to follow dynamic changes in congestion because their pattern of production and release is too slow to reliably mirror hemodynamic variations, having a baseline BNP concentration may help determine a patient's "best" level and may be helpful in optimizing therapy.

Another potential method to assess the development of pulmonary congestion is to measure intrathoracic impedance. Intrathoracic impedance has been inversely correlated with PCWP and fluid balance. This device provides an early warning of congestion that may allow physicians to intervene by adding or titrating medications, possibly preventing the need for hospitalization.³⁶

The "gold standard" for evaluating congestion in hospitalized patients is the measurement of PCWP that can closely approximate LV filling pressure, detecting hemodynamic congestion in its preclinical state. However, PCWP measurement involves invasive catheterization, limiting its clinical use especially in the outpatient setting.

ELEVATIONS IN PULMONARY CAPILLARY WEDGE PRESSURE

An increase in PCWP in normal subjects has been shown to initiate several reflexes, including attenuation of the release of arginine vasopressin, and leads to a water diuresis that is abolished by vagotomy, the so-called Henry-Gauer reflex.³⁷

Other responses to an increase in PCWP result in a decrease in renal sympathetic tone and an increase in natriuretic peptides.^{38,39} These atrial-renal reflexes, which normally enhance renal sodium and water excretion, are impaired in HF because renal sodium and water retention occurs despite elevated PCWP. Experimental HF in dogs has been shown to be associated with a blunting of the atrial-renal sympathetic reflex⁴⁰; in another study, although the elevated plasma vasopressin concentrations were suppressed somewhat with an increase in PCWP, the plasma levels of this antidiuretic hormone remained above normal and no diuresis occurred.⁴¹

High PCWPs have been associated with volume overload in patients with HF and have also been correlated to some extent with more severe symptoms and lower survival rates.^{20,22,42–44} In a study of 1,156 patients hospitalized with acute decompensated HF, those with persistently elevated PCWP >18 mm Hg had increased 1-year mortality compared with those with PCWP <16 mm Hg (34.9% vs. 18.0%).⁴⁵ Investigators have also demonstrated that acute reduction of PCWP with vasodilator therapy can improve cardiac function and reduce mortality risk,^{46,47} suggesting that PCWP is an appropriate marker of cardiac risk and functional improvement. The value of PCWP as a prognostic tool or marker of disease severity or improvement might be explained by the relation of PCWP to LV wall stress. Increased LV wall stress is an important factor in disease progression in HF, because LV wall stress exacerbates myocardial remodeling.^{48–50}

The myocardial remodeling and hypertrophy characterized by increased LV wall stress is eventually unable to compensate for the pathologic increase in pressure and volume load. This ultimately results in the diagnosis of a dilated, failing heart. Increased cardiac troponins have been

reported in patients with LV hypertrophy, suggesting that myocardial damage has occurred and that an unfulfilled oxygen demand may be responsible, in part, for limiting the compensation effect achieved through remodeling.

SUMMARY

The vast majority of hospitalizations for AHFS are related to clinical congestion rather than to a low cardiac output state. Patients develop hemodynamic congestion several days to weeks before the onset of symptoms and signs.

Congestion increases the LV wall stress and contributes to neurohormonal activation. Congestion may lead to LV remodeling, thereby contributing to HF progression. Pulmonary congestion is of major prognostic importance in patients with AHFS and is an important predictor of both mortality and morbidity.

As a result, congestion is an essential evaluative and therapeutic target in patients with AHFS. Studies are needed to evaluate the effect of early identification of congestion on outcomes in patients with AHFS. Even if diuretics are currently the cornerstone of therapy for congestion in patients with AHFS, they are often insufficient to relieve symptoms and are associated with adverse effects. Thus, new therapeutic modalities must be investigated.

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