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Acute Heart Failure: Patient Characteristics and Pathophysiology

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Abstract

The number of hospitalizations for acute heart failure (HF) continues to increase and it remains the most common discharge diagnosis among Medicare beneficiaries. Prognosis after hospitalization for HF is poor, with high in-hospital mortality and even higher post-discharge mortality and rehospitalization rates. It is a complex clinical syndrome that varies widely with respect to clinical presentation and underlying pathophysiology. This paper reviews what is documented in the literature regarding the known pathophysiologic mechanisms reported in patients hospitalized for HF.

Keywords

heart failure; hospitalization; acute; pathophysiology; endothelial function

INTRODUCTION

The importance of heart failure (HF) hospitalizations is well recognized. There are over a million hospitalizations for HF annually in the United States, and they represent a turning point in the natural history of HF with a combined mortality and readmission rate of 30% within 90 days of discharge; a quarter of patients are readmitted within 30-days and 30% die within a year of hospitalization [1]. Hospitalizations are responsible for the majority of the \$39 billion spent annually for HF care [1]. Over the last decade, many therapies have been evaluated in patients hospitalized for HF, with hundreds of millions of dollars invested. Despite positive signals in Phase II studies, none of these therapies have proven to reduce mortality or readmission rates [2•]. The reasons for this are multi-factorial, including drug effects, disease classification, patient selection, and trial conduct [3]. These hospitalizations represent a heterogeneous group of patients, the taxonomy is complex and remains without a consensus, and various terms have been used to describe the condition, including “acute HF”, “acute decompensated HF”, “acute HF syndromes”, and “hospitalized HF” [3–5]. Most studies have focused on treatment during the early phase of hospitalization for HF, and the interventions implemented were largely acute, in-hospital, short-term interventions. Interestingly, most of the deaths in these patients even in the first 30 days are not during the index hospitalization but subsequent to discharge. There remains uncertainty about the

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Conflict of Interest

Catherine N. Marti, Vasiliki V. Georgiopolou, and Andreas P. Kalogeropoulos declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

mechanisms that are related to acute HF. In this article, we review what is known about patient characteristics and pathophysiology of acute HF.

PATIENT CHARACTERISTICS

We selected recent clinical trials and registries that provide insights into the clinical profile of acute HF patients. Data from the Acute Decompensated Heart Failure National Registry (ADHERE) [6] and the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) [7] registries provide insights into acute HF in a non-clinical trial setting, whereas the recently concluded Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) [8••] has generated important information about acute HF patients enrolled in a clinical trial.

Demographics

Demographic and clinical characteristics for patients from ADHERE, OPTIMIZE-HF and ASCEND-HF are shown in Table 1 [6–8]. In general, the mean age of patients enrolled in clinical trials for acute HF was younger than registry data. However, there was considerable overlap in the age range for these patients with a larger proportion of older patients. Similar overlap between racial and gender distribution was noted without any specific demographic predilection.

Comorbidities

Women admitted with acute HF appear to have less coronary disease and more hypertension than men, but a similar rate of atrial fibrillation (30%), diabetes mellitus (40%) and anemia (35%) [6, 9, 10]. Compared to white patients, blacks with acute HF are younger, less likely to have documented evidence of ischemic heart disease, and more likely to have hypertension [11]. Overall however, data from clinical trials and registries show that the distributions of the various common comorbidities that are frequently seen in the population are similarly present among patients with acute HF.

Signs and Symptoms

Dyspnea is the most common symptom reported by patients with acute HF, regardless of severity, followed by fatigue. Systolic blood pressure is higher among those enrolled in acute HF registries than those enrolled in clinical trials. Whether high blood pressure is the cause of HF worsening or a result of acute HF and neurohormonal activation is not clearly known, but it nevertheless provides a therapeutic target in ‘real-life’ acute HF patients. It is not surprising that 64% of those enrolled in OPTIMIZE-HF had rales on exam, as in acute HF the increased pulmonary capillary wedge pressure overwhelms even the hypertrophied lymphatics present in patients with HF chronically. Other signs like peripheral edema are also common.

PATHOPHYSIOLOGY

This section reviews the pathophysiologic mechanisms that have been attributed to or accompany acute HF.

Cardiac Structure and Function

Patients hospitalized for HF represent various phenotypes in terms of cardiac structure and function, including a left ventricular ejection fraction that varies from normal to severely depressed. Of note, lower ejection fraction is associated with worse outcomes, with risks converging above a left ventricular ejection fraction of 45–50% [12, 13]. Similarly, right ventricular dysfunction is associated with increased mortality [14, 15]. Left atrial

enlargement and mitral regurgitation are of prognostic significance as well [16]. Mild to moderate functional mitral regurgitation is seen in 49% and severe in 24% of patients with HF [17] and is known to improve after treatment for acute decompensation [18]. Other valvular abnormalities are common as well [19].

Hemodynamics

Patients with acute HF show a wide range of hemodynamic abnormalities from normal to severely abnormal filling pressure, afterload, and cardiac output. Among patients with acute HF in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, mean pulmonary capillary wedge pressure at the time of hospitalization was 25 ± 9 mmHg while mean cardiac output was 3.8 ± 1.2 L/min [20]. After a median treatment period of 1.9 days, pulmonary capillary wedge pressure and cardiac output were improved: 17 ± 7 mmHg and 4.8 ± 2.1 L/min, respectively [20].

Neurohormonal Activation

While increased neurohormonal activation may be helpful for limited periods, the deleterious effects of excessive and prolonged activation is central to HF progression [21]. *Renin Angiotensin Aldosterone System* activity is increased in HF and among hospitalized patients elevated levels of renin and aldosterone activity is known [22–24]. *Sympathetic nervous system* alterations in acute HF including higher levels of circulating norepinephrine, which correlates with severity of cardiac dysfunction and mortality, has been reported [25–27]. *Arginine vasopressin* concentrations are associated with HF severity [28, 29]. However, arginine vasopressin is difficult to measure. Copeptin, the C-terminal segment of pre-pro-vasopressin, is a stable and reliable surrogate for vasopressin concentrations [30]. It has been associated with increased 90-day mortality and readmissions post discharge [31•]. *Endothelin-1* has vasoconstriction and sodium retention properties and is elevated in hospitalized patients [32–34]. *Adrenomedullin* is a peptide hormone with hypotensive, natriuretic, and inotropic effects. It is elevated in hospitalized patients and has been shown to predict 30-day mortality [35].

Myocyte Damage

Multiple studies have now examined the prevalence of cardiac troponin (cTn) elevation in HF [36]. Elevation of cTn levels is more marked in patients with advanced HF and during admission [37–39]. In the ADHERE registry, 75% of hospitalized patients had detectable troponin levels [40]; and was associated with in-hospital mortality risk.

Inflammation

Inflammation is of pathophysiologic and prognostic significance in acute HF patients. *Tumor necrosis factor* is associated with cardiac structural and functional alterations, including fibrosis, remodeling, and apoptosis [41]. Its levels are elevated in HF, and correlate with severity of cardiac impairment and mortality [42, 43]. *C-reactive protein* levels rise during hospitalization and decrease as the signs and symptoms improve [44]. *Interleukins* are mediators of HF pathogenesis. Interleukin-1 depresses myocardial contractility, inhibits myocyte responsiveness to α -adrenergic stimulation, and promotes apoptosis [45]. Interleukin-6 levels are high during hospitalization and decrease after resolution of symptoms [46, 44, 47–52]. *ST-2 receptor* gene encodes a protein that is a member of the interleukin-1 receptor family and consists of both a trans-membrane receptor form and a truncated, soluble receptor form that can be detected in serum [53]. ST2 concentration during hospitalization correlates with disease severity, myocardial stretch, and inflammation and is associated with prognosis [54].

Oxidative Stress

During hospitalization for HF, excess reactive oxygen species react with nitric oxide (NO), disrupting physiologic signaling and leading to production of toxic and reactive molecules, notably peroxynitrite [55]. *Urine isoprostane* and *plasma aminothiols* [56, 57] are increased during hospitalization [58], unfavorably shifting the nitroso-redox balance and the ventricular and vascular effects of NO. *Myeloperoxidase* is released from activated neutrophils and monocytes as part of the inflammatory process [59] in response to oxidative stress [60]. Myeloperoxidase contributes to vascular inflammation by depletion of vascular NO, which contributes to endothelial dysfunction [61, 62]. Myeloperoxidase levels are increased in both hospitalized and in chronic HF patients [62–64]. *Uric Acid* is a product of xanthine oxidase. Apoptosis and tissue hypoxia lead to increased purine catabolism that in turn increases xanthine oxidase activity and subsequently serum uric acid levels. In patients hospitalized for HF, hyperuricemia is a long-term prognostic marker for death or readmission [65].

Extracellular Matrix Regulation

The dynamic fluidity of the extracellular matrix is maintained by two families of molecules; the *matrix metalloproteinases* (MMPs) that degrade fibrillar collagens, and the *tissue inhibitors of metalloproteinases* (TIMPs) [66, 67]. In the heart, the collagenase (MMP-1) degrades structural collagens, the gelatinases (MMP 2 and 9) degrade basement-membrane components and gelatins, and the stromelysins (MMP 3 and 10) have broad substrate specificity [67, 68]. In patients hospitalized for HF, levels of MMPs are increased, however levels of MMP-2 decrease rapidly with treatment [69•]. Patients with more rapid decreases in MMP-2 levels have better outcomes [69, 70]. *Galectin-3*, a α -galactoside-binding lectin produced by macrophages plays an important role in fibroblast activation and fibrosis [71]. Its expression occurs early in the progression of HF [71]. Galectin-3 is a useful marker for evaluation of patients hospitalized for HF [72] and predicts mortality [73•].

Natriuretic Peptides

B-type natriuretic peptide (BNP) is synthesized in ventricular myocardium and released in response to ventricular dilatation and pressure overload [74, 75]. BNP is derived from an intracellular 108-amino-acid precursor that is cleaved into 2 fragments, yielding a 76 amino acid N-terminal fragment (NT-proBNP) and 32 amino acid BNP [74]. Levels of natriuretic peptides are elevated in acute HF, correlate with functional class, and are independent predictors of prognosis [76]. Baseline and change in natriuretic peptides over time have prognostic usefulness [27, 77]. In the ADHERE registry, median BNP levels in patients admitted with HF was 840 pg/ml [78].

Renal Function

Abnormalities in renal function are common and associated with outcomes in hospitalized HF patients. The clearance of *blood urea nitrogen* is determined by the glomerular filtration rate and tubular reabsorption of urea. Neurohormonal activation leads to increased tubular urea reabsorption and decreases in the glomerular filtration rate [79, 80]. Several studies have shown that elevated blood urea nitrogen is associated with adverse outcomes during hospitalization [81–84]. HF registries have reported lower *creatinine* levels in chronic HF (1.4 ± 2.2 mg/dl) than during hospitalization (1.8 ± 1.6 mg/dl) [85, 6, 9]. Dynamic worsening creatinine is associated with adverse outcomes also [86]. *Cystatin C* is a cysteine protease inhibitor that is unaffected by age, sex, or muscle mass and is more sensitive to mild decreases in glomerular filtration rate. Higher cystatin C levels are associated with increased mortality in hospitalized HF [87•]. *Neutrophil gelatinase-associated lipocalin* is a glycoprotein released by tubular cells during inflammation or injury and its levels are

elevated in HF and correlate with functional class [88]. In patients hospitalized for HF, elevated neutrophil gelatinase–associated lipocalin levels are predictive of worsening renal function [89•]. *Kidney Injury Molecule-1* is a transmembrane glycoprotein whose expression is increased within 24–48 hours after renal injury [90]. It also predicts worse outcome during hospitalization [91].

Endothelial Dysfunction

Increasing HF severity is associated with NO imbalance and endothelial dysfunction. Decreased coronary endothelium-dependent vasodilator capacity impairs myocardial perfusion, reduces coronary flow and worsens ventricular function [92]. The dysfunctional endothelium contributes to increased vascular stiffness and impaired arterial distensibility, augmenting myocardial damage [93]. NO-dependent regulation of ventricular function and vascular tone also determines hemodynamic status during HF hospitalization. Decreased NO availability induces vasoconstriction and increased vascular stiffness in the systemic and pulmonary circulation, resulting in augmented left and right ventricular systolic workload. Decreased NO bioavailability enhances endothelin-1 induced vasoconstriction [94], increases sympathetic outflow and catecholamine release [95], and diminishes sodium excretion in the kidney [96], all of which are important in patients hospitalized for HF.

Epidemiologic Paradox

Traditional risk factors of a poor outcome in the general population, including body mass index, serum cholesterol, and blood pressure, also relate to outcomes but in the opposite direction [97, 98]. In patients hospitalized for HF, akin to chronic HF patients, mortality decreases in a near-linear fashion across higher body mass index quartiles. Similarly, hypercholesterolemia and higher blood pressure are associated with greater survival among patients hospitalized for HF [99, 100]. These findings are in contrast to the well-known associations of over-nutrition, hypercholesterolemia, and hypertension with a poor outcome in the general population [97].

CONCLUSION

To date, many pathophysiologic mechanisms have been described in patients with acute HF. However, what is missing is a clear understanding of (a) how do these abnormalities get exacerbated in chronic HF leading to decompensation; (b) how they are inter-related; (c) what is the sequence of changes in these pathophysiologic mechanisms; (d) how can we define the various sub-populations of acute HF patients based on these mechanisms; and (e) most importantly, how this information can guide development of personalized therapies for patients with acute HF. Further research is needed to take this information from descriptive associations to impact novel therapy development in order to improve outcomes of these patients.

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Table 1

Characteristics of Participants in Recent Registries and Trials of Acute Heart Failure

Characteristic	OPTIMIZE-HF (2003–2004)	ADHERE (2001–2003)	ASCEND (2007–2010)	
N	48,612	105,388	7,007	
Demographics			Nesiritide (N=3496)	Placebo (N=3511)
Age, years	73.1 (14.2)	72.4 (14.0)	67 (56–76)	67 (56–76)
Female, n (%)	25,537(52.0)	(52)	1167(33.4)	1224(34.9)
Black, n (%)	8608(18.0)	(20)	513(14.7)	527(15.0)
Heart Failure Characteristics				
Ischemic etiology, n (%)	22,219(46.0)	-	2081(59.5)	2133(60.8)
Left ventricular ejection fraction, %	39.0(17.6)	34.4(16.1)	-	-
Ejection fraction <40%, n (%)	20,118(48.8)	25,649/40,713(43.0)	2127/2632 (80.8)	2106/2649 (79.5)
Comorbid Conditions				
Atrial fibrillation, n (%)	14,970(31.0)	(31)	1306(37.4)	1322(37.7)
Chronic kidney disease, n (%)	9,515(20.0)	(30)	-	-
Diabetes, n (%)	20,193(42.0)	(44)	-	-
Hypertension, n (%)	34,479(71.0)	(73)	2510(71.8)	2548(72.6)
Physical exam				
Systolic blood pressure, mmHg	143(33.2)	144(32.6)	123(110–140)	124(110–140)
Heart rate, beats/min,	87(21.5)	-	82(72–95)	82(72–95)
Laboratory Tests				
Serum sodium, mEq/L	137(11.0)	-	139(136–141)	139(136–141)
Creatinine, mg/dL	1.8(1.8)	1.8(1.6)	1.2(1.0–1.5)	1.2(1.0–1.6)
B-type natriuretic peptide, pg/mL	1273(1330.1)	-	994(544–1925)	989(543–1782)
Therapy				
ACE inhibitor or angiotensin receptor blocker, n (%)	24,977(52.0)	(53)	2088(59.7)	2168(61.8)
Beta-blocker, n (%)	25,800(53.0)	(48)	2005(57.4)	2069(58.9)
Loop diuretic, n (%)	29,683(61.0)	(70)	3316(94.9)	3347(95.3)
Aldosterone Antagonists, n (%)	3449(7.0)	-	960(27.5)	990(28.2)

Data presented as mean (standard deviation) or median (interquartile range) as appropriate. ACE=angiotensin converting enzyme.