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Latest update

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Acute heart failure: Epidemiology, classification, and pathophysiology

Chapter:

Acute heart failure: Epidemiology, classification, and pathophysiology

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Update:

Acute heart failure: Epidemiology, classification, and pathophysiology

14 new references; 3 new further readings

Updated 3 Tables and 1 Figure

Updated on 22 Feb 2018. The previous version of this content can be found **here**.

Contents

Introduction
Epidemiology
- Epidemiological studies in AHF
- Clinical profile
- Outcomes and prognosis

Classification
- Acute heart failure classifications
- General heart failure classifications relevant for AHF

Pathophysiology
- Main pathogenetic mechanisms
- Congestion
- “Cardiac” versus “vascular” failure
- Myocardial injury
- Renal dysfunction

Conclusion
Further Reading
Full List of References

Introduction

Acute heart failure (AHF) is generally defined as the rapid development or change of symptoms and signs of heart failure that requires urgent medical attention [1].

Overall, AHF is a prevalent condition, as it represents the first reason for hospitalization in advanced age. Furthermore, AHF is a condition with an adverse prognosis, characterized by high mortality and rehospitalization rates. Finally, AHF represents a significant financial burden to health systems, as the enormous health care expenditure required for heart failure is mainly related to hospitalizations for AHF. Impressively, despite the considerable public health and financial burden related to AHF and the advances accomplished in chronic heart failure, there has been only

little progress in the medical management of those patients over the last years, as most of the drugs that have been investigated failed to improve prognosis.

Epidemiology

Epidemiology

Acute heart failure represents the first reason for hospitalization in individuals aged 65 years or older in the Western world, accounting for more than 1 million hospitalizations per year in the US [2]. Over the last few years, several HF registries from different parts of the world were published, providing us with an important bulk of evidence on the epidemiology of the syndrome. Interestingly, these registries do not concern only Europe and US, as it was the case some time ago, but also different parts of Asia and Africa, thus allowing a better understanding of the global epidemiology of acute HF. A number of large-scale registries performed mainly in the US and Europe over the last decade have depicted the epidemiology of AHF providing a picture much closer to the real life situation, see Table 51.1 (3–17).

Table 51.1 Main features and findings of large-scale registries in acute heart failure

	ADHERE	OPTIMIZE-HF	EHFS I	EHFS II	ESC-HF Long-term	ATTEND	CHINA-HF	Gulf CARE	THESUS	ALARM-HF
Study characteristics										
N. of patients	105,388	48,612	11,327	3,580	5,039	4,842	13,687	5,005	1,006	4,953
Region	US.		Europe			Asia			Africa	International
N. of countries	1	1	24	30	21	1 (Japan)	1 (China)	7 (Gulf countries)	9	9
Time period	2001-2004	2003-2004	2000-2001	2004-2005	2011-2013	2007-2011	2012-2015	2012	2007-2010	2006-2007
Patient characteristics										
Age, mean (SD), years	72 (14)	73.1 (14.2)	71	69.9 (12.5)	71 (median)	73 (13.8)	65(15)	59 (15)	52.3 (18.3)	66-70 (median)

Gender, male	48%	48%	53%	61%	62.7%	58%	59.1%	63%	49.2%	62%
Known heart failure	75%	87%	65%	63%	54.5%	36.2%	45.5%	55%		64%
Cardiogenic shock	2%		<1%	3.9%				8%		11.7%
ICU/CCU admission	19%		7%	51%				8.5%		75%
Preserved LVEF (cutoff used)	40% (≥40%)	51% (≥40%)	55% (≥40%)	34% (≥45%)	32.8% (>45%)	46.6% (>40%)	36% (≥45%)	31% (>40%)		25% (≥45%)
Outcomes										
In-hospital mortality	4%	4%	6.9%	6.7%	4.9%	6.4%	4.1%	6.3%	4.2%	11%
Hospital stay, median, days	4	4	11	9		21	10	7	7	6

30 to 90-day post-discharge mortality	11.2% (30 days)	9% (60–90 days)	6.6% (90 days)					12.6% (90 days)	10.6% (60 days)	
1-year post-discharge mortality	36%				23.6			20.2%		
Post-discharge readmission (time period)	22.1% (30 days) 65.8% (1 year)	30% (60–90 days)	24% (90 days)		22.2% (1 year)			18% (3 months) 40% (1 year)	9.1% (60 days)	

Some important AHF registries include:

- The ADHERE (Acute Decompensated Heart Failure National Registry) is performed in the US and constitutes the hitherto largest AHF registry. In 2005, the results on the first 105 388 patients enrolled from 274 hospitals were reported, while an additional report with epidemiological data on a different 104 880 patient cohort was released in 2010 [3–5].
- The OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) was also performed in the US and recruited 48 612 patients from 259 hospitals [6].
- The EuroHeart Failure Survey I was organized by the ESC and recruited 11 327 in 115 hospitals from 24 European countries [7, 8].
- The ALARM-HF (Acute Heart Failure Global Survey of Standard Treatment) was an international retrospective registry that recruited 4953 patients in 666 hospitals from nine countries, including six European ones, plus Turkey, Mexico, and Australia [10].
- The ESC-HF (European Society of Cardiology-Heart Failure) Pilot registry of the ESC Heart Failure Association was part of the EuroObservational Research Program launched by the ESC and recruited 5118 patients in 136 hospitals from 12 European countries, including 1892 patients with AHF and 3226 with chronic heart failure [11].
- The Japanese Acute Decompensated Heart Failure Syndromes (ATTEND) registry enrolled 4842 AHF patients from 53 hospitals in Japan [12].
- The Sub-Saharan Africa Survey of Heart Failure (THESUS-HF) was a prospective survey that enrolled 1006 AHF patients admitted in 12 university hospitals in nine African countries [13].

Clinical profile

The mean age of patients presenting with AHF in the different registries ranges between 70 and 73 years (see Table 51.1). About half of the patients are male. The majority (65–75%) have a known history of heart failure. Most of them have normal or increased blood pressure, while patients presenting with hypotension is generally less than ≤8%, including patients with cardiogenic shock (CS) that represent less than ≤1–2% of cases.

A significant number of AHF patients do not have impaired LVEF. The prevalence of preserved LVEF ranges, in different cohorts, from 25% in the ALARM-HF registry to 55% in the EuroHeart Failure Survey I, depending apparently on the particular clinical features of each population and the applied left ventricular ejection fraction (LVEF) cut-off (see Table 51.1). A comparison of patients with preserved and reduced

LVEF in the OPTIME-HF registry showed that patients with preserved LV systolic function were older and more frequently female, had less frequently an ischaemic aetiology of heart failure, a higher occurrence of risk factors and comorbidities, such as arterial hypertension or diabetes mellitus, and a lower level of NPs [14]. Most of these findings did not differ, whether a 40% or 50% LVEF cut-off was used for patients' classification.

Patients presenting with AHF suffer from several other conditions, besides heart failure. Comorbid states are roughly divided into cardiovascular and non-cardiovascular ones. Cardiovascular comorbidities may often have a causal relationship with AHF, in contrast to extracardiac ones, which are rarely the cause of heart failure but may frequently affect its clinical course and contribute to its worsening or progression. The most prevalent comorbidities in patients with AHF are presented in Table 51.2 and Table 51.3. The cardiovascular history comprises arterial hypertension in about 70% of patients, documented CAD in 50–60%, and AF in 30–40%. Non-cardiovascular comorbidities include diabetes mellitus in about 40% of patients, renal dysfunction in 20–30%, COPD in 20–30%, and anaemia in 15–30%. It should be stressed here the impressively low prevalence of ischaemic heart disease in the sub-Saharan African populations (7.7%) where the primary cause of heart failure was arterial hypertension [12].

Table 51.2 Common comordid conditions in patients with acute heart failure

Common comorbid conditions	
Cardiovascular	• Coronary artery disease • Arterial hypertension • Arrhythmias (i.e., atrial fibrillation) • Valvular heart disease (i.e., mitral regurgitation)
Non-cardiovascular	• Diabetes mellitus • Renal dysfunction • Chronic obstructive pulmonary disease • Anemia • Depression • Cerebrovascular disease • Sleep disordered breathing • Cachexia

Table 51.3 Medical history reported in patients with acute heart failure by large-scale registries

	ADHERE	OPTIMIZE-HF	EHFS I	EHFS II	ESC-HF Long-term	ATTEND	CHINA-HF	Gulf CARE	THESUS	ALARM-HF
N. of patients	105,388	48,612	11,327	3,580	5,039	4,842	13,687	5,005	1,006	4,953
Arterial hypertension	72%	71%	53%	62.5%	64.5%	69.4%	50.9%	61%	55.5%	70.2%
Coronary artery disease	57%	50%	68%	53.6%	54%	31.1%	49.6%	47%	7.7%	30.7%
Diabetes mellitus	44%	42%	27%	32.8%	38.9%	33.8%	21%	50%	11.4%	45.3%
Atrial fibrillation	31%	31%	43%	38.7%	44%	39.6%	24.4%	12%	18.3%	24.4%
Renal dysfunction	30%	30%	17%	16.8%	26.4%				7.7%	21.4%

COPD	31%	28%		19.3%	20.2%	9.5%				24.8%
Anemia				14.7%					15.2%	14.4%

COPD: Chronic Obstructive Pulmonary Disease

Outcomes and prognosis

In-hospital and post-discharge mortality

AHF is a syndrome with ominous prognosis. In-hospital mortality ranges from 4% in American registries to 7% in European surveys [3–9]. An in-hospital mortality rate as high as 11% was reported by the ALARM-HF registry, a survey that included, however, a much higher percentage of critically ill patients i.e., with cardiogenic shock [10]. Post-discharge mortality rates during the first 3 months range between 7% and 11% [4, 7, 8], while mortality at 1 year after the index hospitalization reaches 36% [4]. The median length of hospital stay was 4 days in the American registries and 6–11 days in the European surveys [3, 6, 11], while a much longer median hospital stay of 21 days was reported by the Japanese registry [12]. The cause of death is not always directly related to heart failure. In fact, data from the EVEREST trial showed that the cause of death was directly related to heart failure in 41% of cases, while other causes included sudden death (26%), other cardiovascular causes (5%), and non-cardiovascular ones (13%) (see Figure **51.1**) [15].

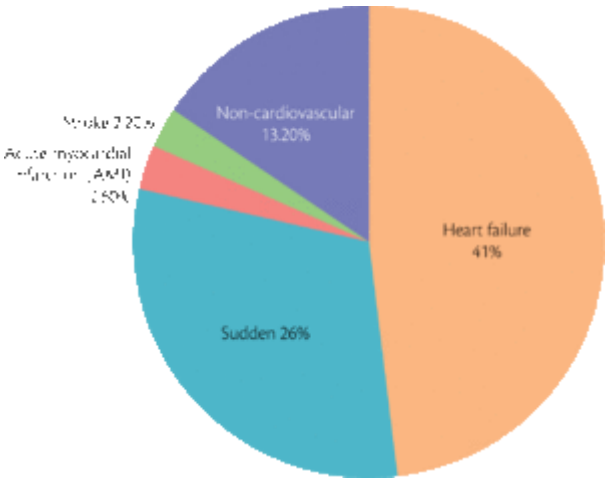

Figure 51.1
Causes of death in patients hospitalized for AHF in the EVEREST trial [Plotted using data from O'Connor et al., *Am Heart J* 2010 [15]].

Readmission to hospital

Discharged AHF patients suffer a considerably high readmission rate. Registries have shown that the incidence of rehospitalization ranges between 22 and 30% at 1–3 months and reaches 65% at 1 year of the index AHF hospitalization [4, 6, 8]. It has been shown that the risk of readmission follows a three-phase pattern, with an early and a late peak, separated by a long plateau phase of low incidence (Figure **51.2**) [16]. According to a Canadian cohort of 8500 patients hospitalized for heart failure and followed subsequently for 10 years, the incidence of recurrent

hospitalization was 30% during the first two months after discharge, 50% during the last two months before death, and 20% during the inter-current period [17]. In more than 50% of patients, the reason for hospitalization is not heart failure itself. Data from the EVEREST trial, in patients with known systolic heart failure, showed that heart failure decompensation is the reason for hospitalization in only 46% of cases, while other cardiovascular reasons, such as ischaemia or arrhythmias, account for another 15% [15]. The remaining 39% of patients were admitted for non-cardiovascular reasons (see Figure **51.3**).

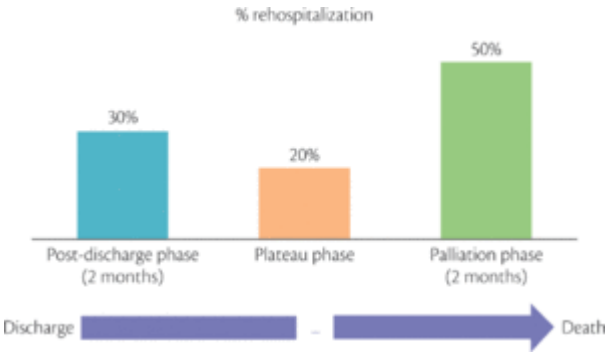

Figure 51.2
Time distribution of post-discharge rehospitalization rate in patients hospitalized for AHF. The incidence of rehospitalization is characterized by two peaks following discharge (post-discharge phase) and preceding death (palliation phase), separated by an inter-current plateau phase [plotted using data from Chun S et al., *Circ Heart Fail* 2012 [22), and Desai AS and Stevenson LW, *Circulation* 2012 [16]].

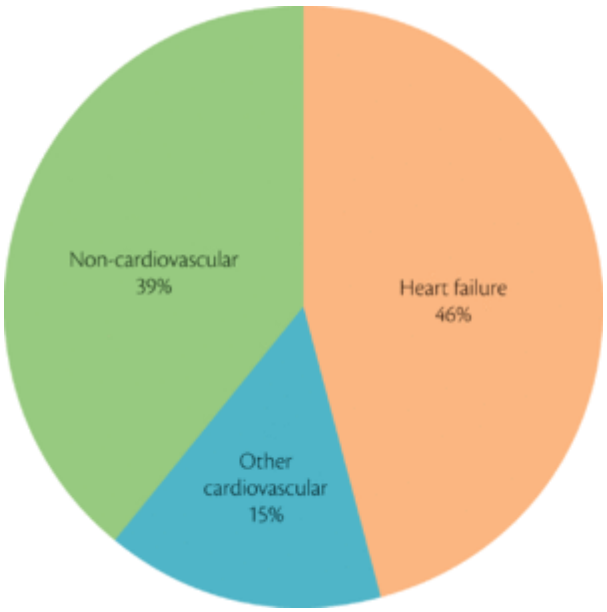

Figure 51.3
Causes leading to hospitalization for acute heart failure in the EVEREST trial [HF: heart failure; CV: ca]diovascular.
Plotted using data from O'Connor et al., *Am Heart J* 2010 [15]].

Recurrent hospital admissions affect adversely and significantly both the clinical course and the health care cost of the heart failure syndrome. It has been postulated that each hospitalization is associated with a deterioration of the cardiac function that is not completely restored to the pre-hospitalization state and the same seems to happen with renal function as well [18]. As a result, recurrent hospitalizations lead to a gradual worsening of the syndrome. This theory is supported by survival data, according to which median survival in heart failure patients decreases gradually with the number of hospitalizations, ranging between 2.5 years in patients with 1 hospital admission to 0.5 year in those with 4 admissions [19]. Regarding cost, it has been calculated that in the United Kingdom, 69% of the total health care expenditure for heart failure is attributable to hospitalizations [20]. In US this is translated into a total cost of $17 billion per year, which represents more than half of the total health care costs for heart failure (2). Given this situation, the US. legislation imposes the reporting of readmission rates during the first 30 days after discharge and establishes a financial penalty for hospitals with the highest readmission rates [21]. Therefore, strategies to prevent rehospitalization in AHF are warranted and involve better decongestion and training of patients during the hospital stay, a timely institution and titration of oral medications, and a close post-discharge monitoring for the early identification and management of decompensation.

Prognostic indicators

Several clinical and laboratory variables are independent predictors of outcome in AHF syndromes. The most important prognostic indicators are presented in Table 51.4.

The systolic blood pressure (SBP) on admission is an important determinant of patients' outcome. Findings from the OPTIMIZE-HF registry show that both in-hospital and post-discharge mortality rates were significantly worse in patients with a lower systolic blood pressure [22]. Thus, in-hospital mortality ranged between 7.2% in patients presenting with a systolic blood pressure of <120 mmHg and 1.7% in those presenting with a systolic blood pressure of >161 mmHg. Similarly, the 2–3-month post-discharge mortality ranged from 14% when the systolic blood pressure on admission was <120 mmHg to 5.4% when the systolic blood pressure was >161 mmHg (see Figure **51.4**). In contrast, the post-discharge readmission rate did not differ significantly according to the admission systolic blood pressure.

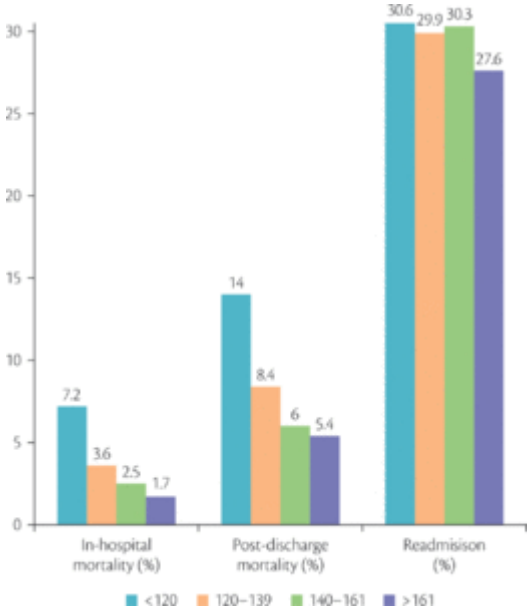

Figure 51.4
Outcome of AHF patients, according to the level of systolic blood pressure on admission in the OPTIMIZE-HF registry. Both in-hospital and 2–3-month post-discharge mortality rates are significantly worse with lower systolic blood pressure (both P <0.001), while the post-discharge readmission rate does not differ significantly
Plotted using data from Gheorghiade et al., *JAMA* 2006 [22].

The LEVF is considered as one of the main determinants of prognosis in heart failure. Patients with preserved LVEF have several clinical differences from those with an established LV systolic dysfunction, as stressed earlier (Table 51.1). However, the prognosis is not quite different between these two subgroups of AHF patients. According to data from the OPTIMIZE-HF registry, although in-hospital mortality was significantly better in patients with preserved systolic function (2.9% versus 3.9% in those with reduced LVEF, LVEF, *P* <0.0001), there was no difference in the post-discharge mortality or hospital readmission at 2–3 months (see Figure **51.5**) [14]. Moreover, the use of neurohormonal inhibitors (angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and β-blockers) at discharge was not associated with a better mortality or readmission rate at 2–3 months in patients with preserved LVEF [14]. This finding is in accordance with the neutral results of several randomized trials on the use of classic heart failure therapies in patients with preserved LVEF.

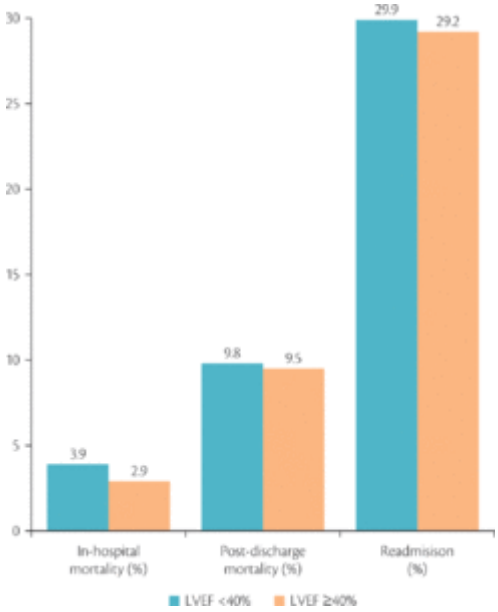

Figure 51.5
Outcome of acute heart failure patients with reduced or preserved left ventricular ejection fraction (LVEF) in the OPTIMIZE-HF registry. Although in-hospital mortality is significantly higher in patients with reduced LVEF ($p<0.0001$), neither post-discharge mortality nor readmission rates at 2–3 mothns differ significantly between the two subgroups
[Plotted using data from Fonarow et al., *J Am Coll Cardiol* 2007 [14]].

In the ALARM-HF registry, in-hospital mortality differed according to the baseline characteristics and comorbid conditions of the patients [10]. For example, mortality ranged from 5% in patients who received renin–angiotensin–aldosterone system (RAAS) antagonists before their hospitalization to 14% in those aged 75 or higher, and to 19% in those with renal dysfunction (see Figure **51.6**).

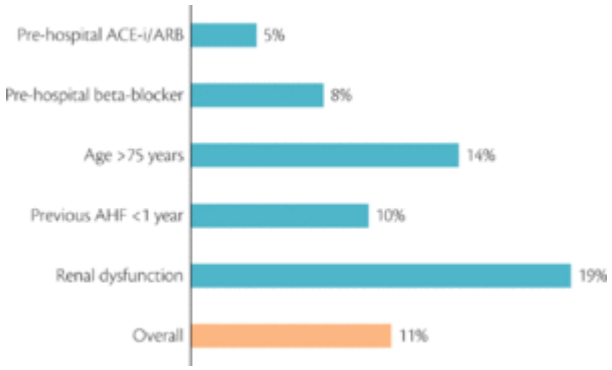

Figure 51.6

In-hospital mortality according to baseline characteristics in the ALARM-HF registry
[Plotted using data from Follath et al. *Int Care Med* 2011 [10]].

The precipitating factors that cause the AHF episode also have prognostic significance. Data from the OPTIMIZE-HF registry showed that in-hospital mortality was relatively low, around 2%, when AHF had been caused by hypertension or a lack of compliance with medications, increased to 4% in the case of myocardial ischaemia, increased further to 6% when AHF had been provoked by pneumonia and reached 8% when the precipitating factor had been a worsening renal function (see Figure **51.7**) [23].

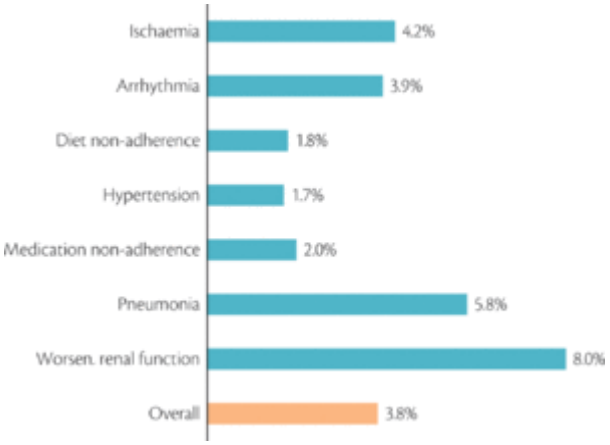

Figure 51.7
In-hospital mortality according to precipitating factors in the OPTIMIZE-HF registry
[Plotted using data from Fonarow et al. *Arch Intern Med* 2008 [23]].

Classification

Acute heart failure classifications

AHF is a rather heterogeneous group of patients, and there have been several attempts to categorize AHF syndromes, using different classification criteria (see Table 51.5). Depending on whether patients have a past history of heart failure or not, AHF is classified into:

- *Acutely decompensated chronic heart failure (ADCHF)*, that occurs in patients with a heart failure history. As stated earlier, ADCHF is far more frequent, representing about 65–75% of patients hospitalized for AHF according to different registries (see Table 51.1). Several precipitating factors (see Table 51.6) act as a trigger of worsening, leading usually to a gradual disruption of the patients' cardiac function

and haemodynamics. Besides cardiac and extra-cardiac conditions, the lack of compliance with prescribed medications is a common precipitating factor, accounting for 22% of ADCHF cases in the EuroHeart Failure Survey II [9].

• *De novo AHF*, that occurs in individuals without a past history of heart failure. This is the case for the remaining one third or less of AHF patients. These patients often have a history of risk factors such as arterial hypertension, diabetes mellitus or advanced age. The term *de novo* AHF has been used to describe the AHF patient with a rapid development of symptoms and signs of heart failure that requires immediate medical care. It has been also incorrectly used interchangeably with the term AHF with preserved ejection fraction. Acute coronary syndromes (ACS) are a frequent cause for the development of the syndrome. In the community, patients could also be presented with symptoms and signs of heart failure for the first time (*de novo*); however, in these patients, the onset is more gradual.

A simple and clinically relevant classification depends on the level of systolic blood pressure (SBP) at presentation. Although the systolic blood pressure cut-off for hypertension is well defined (140 mmHg), it is not the same for hypotension and different cut-offs have been proposed, such as 90 or 85 mmHg. The latest ESC guidelines propose 90 mmHg as the cut-off to recommend the use of inotropes or vasopressors in AHF patients [1]. Thus, AHF is classified into:

• *Hypertensive AHF*, when SBP at presentation is >140 mmHg. These patients represent 50% or more of AHF cases and are more likely to be elderly and female and to have preserved LVEF [24]. Their symptoms' development is usually abrupt and involves pulmonary congestion [25]. The mortality rates in this subgroup are significantly lower, with in-hospital mortality ranging from 1.7–2.5% and post-discharge 2–3-month mortality from 5.4 to 6% [22].

• *Normotensive AHF*, when the systolic blood pressure (SBP) at presentation falls between 90 and 140 mmHg. These patients represent 40% or more of AHF cases and usually have ADCHF and reduced LVEF. Their symptoms' development is usually gradual and involves significant systemic congestion [25]. The in-hospital mortality ranges between 8 and 10% [24].

• *Hypotensive AHF*, when SBP at presentation is <90 mmHg. These patients represent less than 8% of AHF cases [25]. Many of them have advanced or end-stage heart failure and they present with signs of low cardiac output and tissue hypo-perfusion, while some of them present with CS. The in-hospital mortality is higher than 15, reaching 30% or more in the case of CS [24].

This classification is clinically relevant, as the systolic blood pressure on admission is a strong predictor of outcome, particularly of mortality, while it also guides the initial therapeutic decisions (i.e., inotropes/vasopressors

in hypotensive AHF or vasodilators in hypertensive AHF). However, all these the systolic blood pressure cut-offs are arbitrary and clinical evaluation of the patients is very important.

Another clinical classification of AHF patients is based on the hemodynamic condition and more specifically according to whether there are or not signs of congestion and signs of low cardiac output and peripheral hypoperfusion at rest [26]. The patient is characterized as ‘wet’ or ‘dry’ in the presence or absence of congestion, respectively, and as ‘cold’ or ‘warm’ in the presence or absence of signs of low cardiac output. Thus, four categories are possible (see Figure **51.8**):

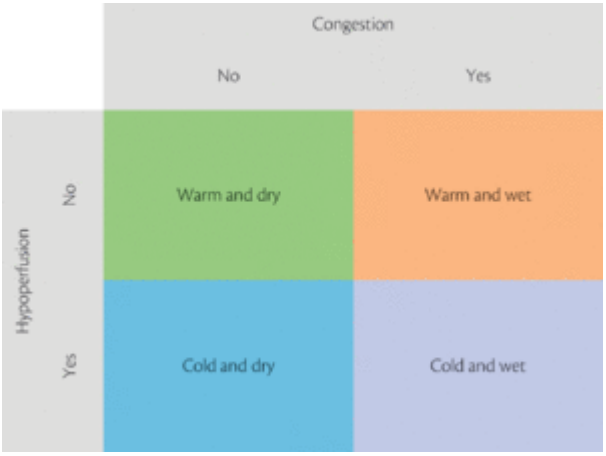

Figure 51.8
Classification of AHF patients, according to the presence or absence of signs of congestion (‘wet’ and ‘dry’, respectively) and the presence or absence of signs of low cardiac output (‘cold’ and ‘warm’, respectively).
From Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 201; 128: 1810–52 with permission from Wolters Kluwer Health.

- Warm and dry (well perfused without congestion)
- Warm and wet (well perfused but congested)
- Cold and dry (hypoperfused without congestion)
- Cold and wet (hypoperfused and congested)

This classification has been used in the past for patients with advanced heart failure, but it is still useful for the initial management of AHF patients.

General heart failure classifications relevant for acute heart failure

The following general heart failure classifications are also relevant for patients with AHF.

The single universally established classification of patients with symptoms of heart failure is that proposed by the New York Heart Association (NYHA)[29]. Patients are classified into four categories according to their functional capacity and the severity of their symptoms:

- *NYHA class I*: no limitation of physical activity. Ordinary physical activity does not cause symptoms of heart failure.
- *NYHA class II*: slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of heart failure.
- *NYHA class III*: marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of heart failure.
- *NYHA class IV*: unable to carry out any physical activity without symptoms of HF, or symptoms of heart failure at rest.

Another classification (1), also used in chronic heart failure, is based on whether LVEF is impaired or not and thus AHF is divided into:

- *Heart failure with reduced LVEF (HFrEF, LVEF<40%),* formerly termed systolic heart failure.
- *Heart failure with mid-range LVEF (HFmrEF, LVEF=40-49%).* The new classification of HF proposed by ESC in the latest guidelines may contribute to the better comprehension and conception of this ‘gray area’ between 40 and 50%; it seems that HF patients in this group represent a distinct group between HFrEF and HFpEF in terms of clinical features [26].
- *Heart failure with preserved LVEF (HFpEF, LVEF>50%)*, formerly termed diastolic heart failure. This group represents approximately half of AHF cases. As stressed earlier, these patients are more likely to be older, female, hypertensive, diabetic and to have non-ischaemic etiology of heart failure [14].

Different LVEF cut-offs for defining preserved LV systolic function have been used, including 40%, 45%, and 50%, and there is not yet a universally accepted one. The AHA and the ACC have lately proposed the following classification of heart failure patients, according to LVEF [26]:

- *HFrEF*: LVEF ≤40%
- *HFpEF*: LVEF ≥50%
- *HFpEF, borderline*: LVEF 41–49%; studies have shown that these patients may have intermediate features between HFrEF and HFpEF but do not differ in clinical profile and outcome from those with HFpEF [14]

• *HFpEF, improved*: LVEF >40%; patients with formerly reduced LVEF who have had a recovery and thus may bear particular features, compared to those with persistently reduced LVEF

This classification is also clinically relevant, as the indicated long-term oral medications differ significantly between the two subgroups; AHF patients with reduced LVEF require timely onset and proper titration of neurohormonal inhibitors (renin-angiotensin-aldosterone system inhibitors and beta-blockers), while those with preserved LVEF are treated by risk factor control and symptomatic therapies.

Pathophysiology

Main pathogenetic mechanisms

Heart failure results from four key pathogenetic mechanisms: (1) volume overload, (2) pressure overload, (3) myocardial loss, and (4) impaired ventricular filling (see Figure **51.9**). Several cardiovascular and non-cardiovascular conditions lead to AHF through a single of the aforementioned pathogenetic mechanisms or a combination of them. For example, the main mechanism causing heart failure during an ACS is myocardial loss, but volume overload or impaired filling may also be involved if ACS is complicated with acute MR or tachyarrhythmia, respectively. These conditions or factors may either provoke a rapid deterioration of the cardiac function and haemodynamics in an individual without a previous history of heart failure, hence leading to *de novo* AHF, or disrupt the previous steady state condition in a patient with known chronic heart failure and cause ADCHF. The most frequent etiologies and precipitating factors that may cause AHF are presented in Table 51.6. Their timely identification and treatment are an important aspect of the management of AHF.

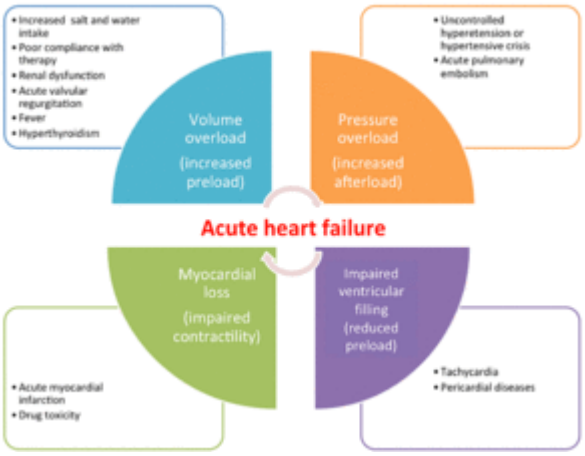

Figure 51.9

Main pathogenetic mechanisms leading to AHF. Examples of causes or precipitating factors are provided for each mechanism.

Congestion

The hallmark of AHF is congestion. Congestion is either peripheral, characterized by weight gain, peripheral oedema, jugular vein distension, hepatic enlargement, and/or pain, hepato-jugular reflux and ascites or pulmonary congestion, characterized by dyspnoea of varying severity and lung rales. Peripheral congestion usually coexists with pulmonary but not always vice versa. The two main mechanisms leading to congestion is fluid retention and fluid redistribution (see Figure **51.10**). In the case of fluid retention, cardiac dysfunction leads to a low cardiac output that, in turn, activates neurohormonal compensatory mechanisms, leading to increased release of aldosterone and arginine vasopressin that cause Na^+ and water retention in the kidneys and thus peripheral and pulmonary congestion. On the other hand, fluid redistribution results from peripheral vasoconstriction; venous constriction causes an increase in the venous return and thus preload, while arterial constriction increases the afterload, both leading in turn to increased LV pressures, increased pressures in pulmonary capillaries, and thus pulmonary congestion.

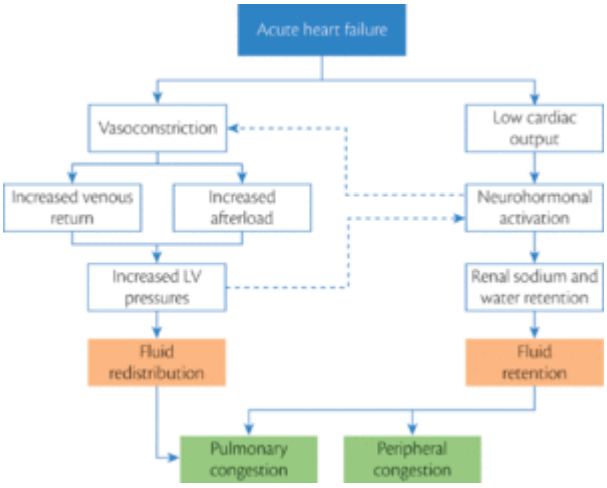

Figure 51.10
Pathophysiology of congestion. The two main pathogenetic pathways of fluid redistribution and fluid retention are interrelated (dotted arrows).

‘Cardiac’ versus ‘vascular’ failure

Taking under consideration the two aforementioned mechanisms causing congestion, a recent approach to the pathophysiology of AHF outlines two different profiles, a central one termed ‘cardiac failure’ and a peripheral one termed ‘vascular failure’ (see Figure **51.11**) [30]. In the case of ‘cardiac failure’, AHF is caused by a deterioration of the cardiac function per se, a mechanism that predominates in ADCHF patients with impaired LVEF and normal or low arterial pressure; the main pathogenetic mechanism causing congestion is fluid retention. In the case of ‘vascular failure’, in contrast, vasoconstriction leading to fluid redistribution is the main cause of congestion, a mechanism seen, for example, in acute pulmonary oedema and hypertensive crisis. These latter patients have frequently preserved LVEF and normal of increased arterial pressure. This consideration of AHF pathophysiology is actually clinically relevant as ‘cardiac failure’ is treated mainly with diuretics and in more severe cases, with inotropes, while ‘vascular failure’ is managed primarily with vasodilators. However, this is a complex syndrome, and the two mechanisms co-exist with different magnitude, in most patients.

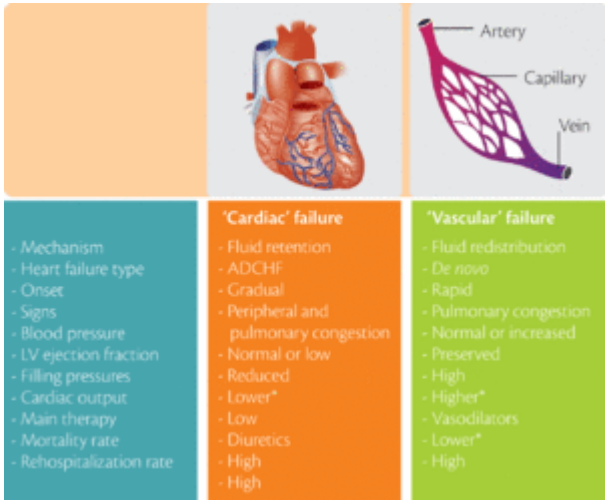

Figure 51.11
Clinical profile and pathophysiology of AHF: ‘Cardiac’ versus ‘vascular’ failure (* compared to ‘vascular’ or ‘cardiac’ failure).

Two important mechanisms contributing to the pathophysiology of AHF are myocardial injury and renal dysfunction. They may often be the cause or a precipitating factor for AHF, but they also constitute the consequences of AHF, that contribute to the further deterioration of the syndrome. Other comorbid conditions, such as anaemia and iron deficiency, play an important role in the pathophysiology and outcome of patients with chronic heart failure, but their role in AHF has not yet been clarified.

Myocardial injury

ACS are a frequent cause of AHF. At the same time, AHF itself is followed by myocardial ischemia that leads to myocardial injury. Indeed, cTn elevation, a surrogate of myocardial injury, is an independent predictor of short and long-term outcome in AHF. Data on nearly 85000 AHF patients from the ADHERE registry published in 2008 showed that, 6% of patients had a positive troponin tests and those patients had a 2.6 times higher risk of in-hospital mortality [31]. On the other hand, In the recently released RELAX-AHF (Relaxin in Acute Heart Failure) trial, in which the new-generation high-sensitivity troponin assays were used, troponin levels were higher than the upper reference limit (URL) in 93% of patients and were independently associated with 180-day mortality, while a further increase of ≥20% during the first 2 days nearly doubled the risk of death [32].

In the context of AHF, ischaemia is caused both by a decrease in the myocardial O2 supply and an increase in the myocardial O2 demand. O2 supply may be impaired due to: (1) low diastolic arterial blood pressure and high LV diastolic pressure, the combination of which leads to a decrease in the coronary driving pressure, and thus impaired coronary perfusion; (2) tachycardia that restricts the diastolic period, and thus the coronary perfusion time; and (3) potentially co-existing coronary artery disease (CAD). O2 demand, on the other hand, is increased because of high LV wall stress, tachycardia, and inotropic therapy [33].

Renal dysfunction

A frequent and important component of AHF pathophysiology is renal dysfunction. Renal dysfunction is a prevalent abnormality in AHF. In the ADHERE registry, among 118 465 patients admitted with AHF, only 9% had normal renal function on admission (glomerular filtration rate (GFR) ≥90 mL/min/1.73 m2);71% had mild to moderate renal dysfunction (GFR 30–89 mL/min/1.73 m2), and 20% had severe dysfunction (GFR <30 mL/min/1.73 m2) [34]. The close interdependence of the heart and kidneys may lead to a vicious circle, in which heart failure causes renal dysfunction that, in turn, promotes an additional deterioration of the cardiac function that aggravates further the renal impairment, and so on. The term ‘cardiorenal syndrome’ has been introduced to express this complex bidirectional relationship [35]. The main mechanisms linking cardiac with renal dysfunction are outlined in Figure **51.12**. In brief, heart failure affects renal function by three main mechanisms [36]: (1) a low cardiac output (forward failure) that leads to a low perfusion pressure in the afferent arteriole of the glomerulus; (2) a high central venous pressure (CVP) (backward failure) that increases the intra-abdominal pressure, and thus the pressure on the Bowman’s capsule; and (3) drug therapy and mainly diuretics that reduce the intravascular volume and thus cause a further decrease in the glomerulus perfusion pressure, and RAAS inhibitors that cause dilatation of the efferent arteriole. The combination of the three mechanisms mentioned leads to low filtration pressure in the glomerulus, and thus a low urine output. At the same time, there are several additional factors with an increased prevalence in heart failure that affect both the cardiac and renal function such as neurohormonal and inflammatory activation, anaemia, necrosis, apoptosis, and fibrosis. Finally, a number of risk factors that are common to heart and renal failure are frequently present in heart failure patients such as diabetes mellitus, hypertension, and ageing.

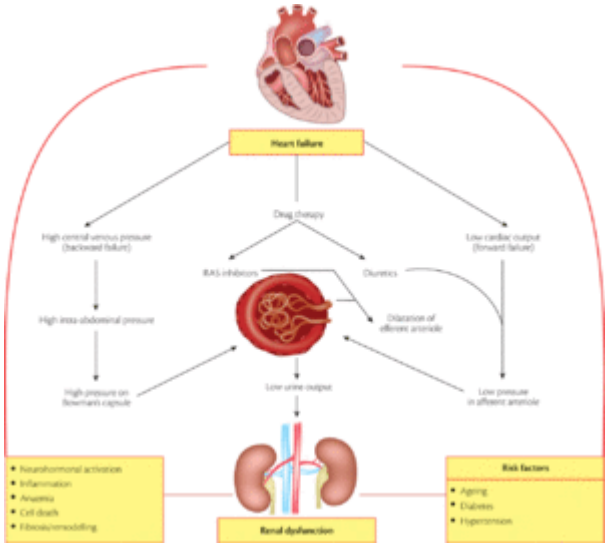

Figure 51.12
Pathogenetic interactions between cardiac and renal function ADHF [Modified with permission from Filippatos et al., *Eur Heart J* 2014 (43)].

Conclusion

AHF represents the most common cause of hospital admission in the elderly and the main contributor to the huge health care costs of heart failure. Despite recent therapeutic advances, the prognosis of the syndrome remains ominous, with 4 to 7% of patients dying during the index hospitalization and one third of them dying or being readmitted within the following few months. The clinical profile of patients upon presentation is heterogeneous and constitutes a significant determinant of in-hospital and post-discharge outcome. The pathophysiology of AHF is complex and involves several mechanisms provoked by cardiac or extra-cardiac causes or precipitating factors leading to congestion and other conditions contributing to the further progression of the syndrome.

Personal Perspective

AHF is the first reason for hospitalization in the elderly and accounts for the vast majority of the total health care cost of heart failure. Despite recent therapeutic advances in cardiovascular medicine, AHF remains a syndrome with a considerably dismal prognosis. A better definition and classification of the syndrome that may result from a more comprehensive understanding of its pathophysiology may allow a more effective management and thus a better outcome for AHF patients.

Further Reading

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