The Clinical Problem: Heart Failure Syndromes and their Epidemiology

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Abstract

Heart failure (HF) is increasing in incidence and is a growing health care burden. HF is responsible for a large proportion of deaths as well as for diverse associated morbidities. Both in-hospital and 1-year outcomes of patients admitted for acute HF (AHF) remain poor. HF can be classified by LVEF, by the time course of its presentation and by its associated symptoms and triggering factors. The population of patients with HF is huge, and prognosis remains poor.

Keywords: heart failure; epidemiology

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Introduction

Heart failure (HF) with its constantly increasing incidence is a growing health care burden in the developed and developing worlds alike. The number of hospitalizations due to HF is still rising, and it has tripled over the last 3 decades. HF is responsible for a large proportion of deaths as well as for diverse associated morbidities, all of which translate into reduced quality of life in patients with HF.[1] Both in-hospital and 1-year outcomes of patients admitted for acute HF (AHF) remain poor, with a particularly high mortality rate.[2]

Definition of heart failure

According to the 2016 ESC Guidelines, HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[3]

The core criterion in the diagnosis is heart pathology causing systolic and/or diastolic ventricular dysfunction, but other abnormalities of valves, pericardium, endocardium, heart rhythm and conduction can also lead to a HF syndrome (and more than one abnormality may be present).[3]

Different classification systems of heart failure syndromes

The use of different classification systems dependent on the context for which they are being used provides a reasonable framework for clinician communication regarding both diagnostic and therapeutic decisions, the monitoring of the progression of HF symptoms and stages and for risk stratification.

Classification based on left ventricular ejection fraction

One fundamental classification of HF is based on the measurement of left ventricular ejection fraction (LVEF), which divides patients into 3 groups: HF with preserved LVEF (LVEF $\geq$ 50%) (HFpEF); HF with reduced LVEF (<40%) (HFrEF) and HF with mid-range LVEF (LVEF in the range of 40–49%) (HFmrEF), previously defined as a 'grey area'. [3] For the diagnosis of HFpEF and HFmrEF, in spite of the presence of signs and symptoms of HF and defined LVEF values, the following criteria are also obligatory: elevated levels of natriuretic peptides: brain natriuretic peptide (BNP) $\geq$ 35 pg/ml and/or N-terminal pro-B type natriuretic peptide (NT-proBNP) $\geq$ 125 pg/mL together with signs of relevant structural heart disease (left ventricular hypertrophy (LVH) and/or left atrial enlargement (LAE)) [4,5,6] and/or signs of diastolic dysfunction.[3-7]

The differentiation of patients with HF based on LVEF is important, especially in the context of different therapeutic options. Moreover, the diagnosis of HFpEF and HFmrEF is

more challenging than the diagnosis of HFrEF, and sometimes requires stress tests, e.g. stress echocardiography, which may facilitate the detection of diastolic dysfunction related to exercise exposure in patients with exertional dyspnoea, preserved LVEF and inconclusive diastolic parameters at rest.[8,9]

HF is most commonly identified with left ventricular (LV) dysfunction, but in some cases right ventricular (RV) HF is diagnosed, either isolated or more commonly accompanying LV dysfunction. The echocardiographic criteria identifying RV dysfunction include: tricuspid annular plane systolic excursion (TAPSE) <17 mm and tissue Doppler-derived tricuspid lateral annular systolic velocity (s') <9.5 cm/s.[6,10] More advanced methods such as three-dimensional speckle tracking echocardiography may be an additional quantitative method to assess RV function in expert centres.[11]

Classification related to the time course of heart failure

The term 'heart failure' is reserved for symptomatic patients, as symptoms are crucial for the diagnosis, and a patient who has never exhibited the typical symptoms and/or signs of HF and has a reduced LVEF is described as having asymptomatic left ventricular (LV) systolic dysfunction.[3] Patients who have had HF for some time are often said to have 'chronic HF' (CHF).[3] However a patient can be rendered asymptomatic by treatment. [3] When there is volume overload in both acute or chronic HF the term 'congestive HF' is often used.[3]

The course of HF can be 'stable', if the symptoms and signs have remained generally unchanged for at least 1 month in treated patients; alternatively a deterioration in clinical status may occur, which is described as a 'decompensation' episode either acute HF (AHF) or acute decompensated HF (ADHF).[3]

AHF is defined as a new onset or a gradual or rapid worsening of HF signs and symptoms, which requires urgent or emergency therapy.[3,12] The hallmark of patients with AHF are phenotypic variations of clinical presentations, even though the vast majority of them present with congestion.[13] AHF encompasses at least 2 clinical distinct entities: (1) worsening chronic HF associated with reduced, mid-range or preserved LVEF – more frequent (about 70% of all admissions); and (2) de novo HF (e.g. after acute myocardial infarction (AMI) for example, or due to a sudden increase in blood pressure superimposed on a noncompliant LV).[12] In the course of AHF the primary aetiology needs to be distinguished from precipitating factors (for details see below).[3]

Decompensation of chronic HF may occur suddenly or slowly, often requiring hospitalization and translating into poor clinical outcomes.[3] New-onset ('de novo') HF may also present acutely, for example, as a consequence of AMI, or in a sub-acute (gradual) fashion, for example, in patients with a dilated cardiomyopathy (DCM) due to myocarditis, who often have symptoms for weeks or months before the diagnosis becomes clear.[3] Usually after the onset of HF, the course of the disease changes into a chronic one, but it is also possible, that the patient may have HF due to a problem that resolves completely (e.g. acute viral myocarditis, Takotsubo cardiomyopathy or tachycardiomyopathy).[3]

Classification related to symptoms

Symptoms of HF are characterized by a different level of specificity. The fundamental symptom is exercise intolerance reflected by exertional dyspnoea and/or fatigue, whereas the key signs are frequently explained by various manifestations of fluid retention.

In addition to dyspnoea (on exercise or at rest), the following symptoms are also described in HF: orthopnoea, paroxysmal nocturnal dyspnoea, fatigue, tiredness, increased time to recover after exercise and ankle swelling.[14-18] Among signs, elevated jugular venous pressure and a laterally displaced apical impulse may be more specific, but are harder to detect.[18,19]

The American College of Cardiology/American Heart Association (ACC/AHA) HF staging approach, based on structural changes and symptoms, emphasizes the importance of the development and progression of disease from predisposing stages to overt HF.[20] The ABCD scale identifies the following patient groups: A - patients at high risk of HF, but without structural heart disease or HF signs/symptoms; B – structural heart disease without HF signs/symptoms; C – structural heart disease with previous or current HF signs/symptoms; D – refractory HF requiring specialized interventions.[20]

The severity of HF symptoms and exercise intolerance are frequently described using the New York Heart Association (NYHA) functional classification.[3] NYHA I class includes patients with no limitation of physical activity (ordinary physical activity does not cause HF symptoms), NYHA II class includes subjects with a slight limitation of physical activity (comfortable at rest, but ordinary physical activity results in HF symptoms), NYHA III class includes patients with a marked limitation of physical activity (comfortable at rest, but less than ordinary activity causes HF symptoms), and NYHA IV class includes patients with advanced HF who are unable to carry on any physical activity without HF symptoms of HF, or/and HF symptoms occur at rest.[3] The NYHA classification scheme is helpful for monitoring of the effectiveness of treatment and for a rough prognosis assessment, although the severity of symptoms does not fully correlate with the degree of myocardial injury.

The clinical classification of patients with AHF based on bedside assessment of clinical symptoms/signs of congestion ('wet' vs. 'dry' profile if present vs. absent) and/or peripheral hypoperfusion ('cold' vs. 'warm' profile if present vs. absent) allows the stratification of subjects with different prognoses and assigns them to groups requiring different therapeutic strategies.[21,22] Congestion signs/symptoms such as pulmonary congestion, orthopnoea, and paroxysmal nocturnal dyspnoea are typical for LV failure, whereas peripheral oedema, jugular venous dilatation, congested hepatomegaly, gut congestion, ascites and a detectable hepatojugular reflux are congestion signs/symptoms related more to RV failure.[3] Signs/symptoms of hypoperfusion include cold sweaty extremities, oliguria, mental confusion, dizziness and a narrow pulse pressure. The combination of these features identifies 4 groups of AHF presentations: 1) 'warm and wet' (well perfused and congested) – the most common presentation; 2) 'cold and wet' (hypoperfused and congested); 3) 'cold and dry' (hypoperfused without congestion); 4) 'warm and dry' (compensated, well perfused without congestion). This classification may be helpful to guide therapy in the initial phase and carries prognostic

information.[21,23,24] 'Wet' and 'warm' patients typically have elevated or normal systolic blood pressure and may be divided into two subtypes: 'vascular type' with fluid redistribution where hypertension and vasoconstriction predominates, and 'cardiac type' with fluid accumulation, where congestion dominates.[3]

The term 'advanced HF' is reserved for patients with HF with severe symptoms, recurrent decompensation episodes and severe cardiac dysfunction.[25] Advanced HF identifies a stage of HF where conventional treatments – pharmacological as well as invasive therapies – are insufficient to control the patient's symptoms, and advanced therapies (e.g. cardiac transplantation) or palliative therapies (e.g. inotropic infusions, ultrafiltration or peritoneal dialysis to control volume, or end-of-life comfort care) are needed.[25,26] The terms 'advanced', 'refractory', and 'end-stage' HF can be used as interchangeable terms to some extent, which may concern patients who should be evaluated for advanced HF therapies.[26]

For the diagnosis of advanced HF, all the following criteria must be present, despite the use of optimal guideline-directed treatment: 1) severe and persistent symptoms of HF [NYHA class III (advanced) or IV]; 2) severe cardiac dysfunction defined as reduced LVEF $\leq 30\%$, isolated RV failure (e.g. ARVC) or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and evidence of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF [3]; 3) episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months; 4) severe impairment of exercise capacity with either an inability to exercise or a low 6-minute walk test distance (6MWT) (<300 m) or peak oxygen uptake (peak VO₂) measured during cardiopulmonary exercise testing (<12 – 14 L/kg/min), of cardiac origin.[25] Extra-cardiac organ abnormalities such as cardiac cachexia, liver, or kidney dysfunction due to HF or type 2 pulmonary hypertension, may be present, but are not required for the diagnosis. Patients who have as well cardiac dysfunction (as described in criterion #2) a substantial limitation due to other conditions (e.g. severe pulmonary disease, non-cardiac cirrhosis, or most commonly by renal disease with a mixed aetiology) can meet criteria #1 and #4. Therapeutic options for these patients are usually more limited compared to those where cardiac disease predominates.[25]

For patients qualified for mechanically assisted circulatory support there is also an INTERMACS classification, which is used for therapeutic decisions also carries prognostic information (see table 1).[26,27]

Classification related to aetiology and factors triggering decompensation

The most common HF aetiology in the western world is ischaemic heart disease (IHD), where HF may occur as a consequence of post-myocardial infarction cardiac remodeling. Importantly, a normal coronary angiogram does not exclude an ischaemic aetiology of HF, which may be due to abnormalities within the coronary microcirculation.[3] Other causes of HF include: hypertension, toxic agents (including drugs and radiation),

immune-mediated and inflammatory damage, infiltration, metabolic derangements, genetic abnormalities and abnormal loading conditions: hypertension, valve and myocardium structural defects, pericardial and endomyocardial pathologies, high output states, volume overload, tachy- and bradyarrhythmias, to name but a few.[3] The identification of HF aetiology is a *sine qua non* condition to implement causally-directed treatment.

In the course of AHF, the primary aetiology needs to be distinguished from precipitating factors. Factors triggering AHF may be in some cases unknown or overlapping, but usually are possible to identify, which is very important for therapeutic decisions. Uncontrolled hypertension, myocardial ischaemia, arrhythmia, exacerbation of chronic obstructive pulmonary disease, pneumonia or other infections, and finally non-compliance to medical instructions (dietary and/or pharmacological) are the major precipitants for AHF.[3] In the OPTIMIZE-HF registry, 61% of enrolled subjects had an identifiable clinical precipitant, with pulmonary processes (15%), myocardial ischaemia (15%), and arrhythmias (14%) being the most common known triggers of AHF.[28]

Cardiomyopathies are defined by structural and functional abnormalities of the ventricular myocardium that are unexplained by flow limiting coronary artery disease or abnormal loading conditions.[29] They are grouped into specific morphological and functional phenotypes (dilated cardiomyopathy [29,30], hypokinetic non-dilated cardiomyopathy [30], hypertrophic cardiomyopathy [31], arrhythmogenic cardiomyopathy [29,32], restrictive cardiomyopathy [29], unclassified cardiomyopathies including e.g. left ventricular non-compaction and Takotsubo cardiomyopathy [29]). Each phenotype is sub-classified into familial and non-familial forms.[29]

Epidemiology of heart failure syndromes: prevalence, incidence and prognosis

Exact data on HF epidemiology from a global perspective are difficult to obtain, as outside Europe and the U.S. few registers are kept that would allow an accurate quantitative description in the terms of occurrence, prevalence and outcomes.

Over 1 million hospitalizations with a primary diagnosis of HF occur each year in the U.S. [33] and a proportionately larger number in Europe [34] with an increase in hospitalization number of over 175% in the last 25 years in U.S.[33,35] The number of emergency department visits for AHF is still growing, and AHF resulting in hospitalization is the most common diagnosis-related group for Medicare patients and in total, the most expensive.[33,36] The financial burden related to heart failure in the U.S. is 34-39 billion dollars per year, mainly related to hospitalizations.[33,35,36]

The population of patients with HF is huge, which is reflected in the numbers: over 5 million Americans and 15 million Europeans suffer from HF [33,36,37], and an estimated extra 26 million people suffer from HF worldwide.[34] The prevalence of HF is still increasing [34] and is estimated to be approximately 1–2% of the adult population in developed countries, rising up to $\geq 10\%$ among people >70 years of age.[38-41] Among people >65 years of age presenting to primary care with breathlessness on exertion, one in six will have an unrecognized HF (mainly HFpEF). [42,43] This unfavourable trend will continue due to the ageing of

Table 1. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles references 26,27.

Profile for interventions	Time Frame
Profile 1: Critical cardiogenic shock Crash and Burn type - including resistant hypoperfusion despite accelerating therapy	Definitive intervention needed within hours
Profile 2: Progressive decline Sliding on inotropes-unresponsive or unable to tolerate inotropic support	Definitive intervention needed within few days.
Profile 3: Stable but inotrope-dependent Dependent stability stable on inotropes, but unable to wean	Definitive intervention elective over a period of weeks to few months.
Profile 4: Resting symptoms Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during ADL. Some patients may shuttle between 4 and 5.	Definitive intervention elective over a period of weeks to few months.
Profile 5: Exertion intolerant Comfortable at rest and with ADL but unable to engage in any other activity, living predominantly within the house.	Variable urgency, depends upon maintenance of nutrition, organ function, and activity.
Profile 6: Exertion limited Patient without evidence of fluid overload is comfortable at rest, and with ADL and minor activities outside the home but fatigues after the first few minutes of any meaningful activity.	Variable, depends upon maintenance of nutrition, organ function, and activity level.
Profile 7: Advanced NYHA class III A placeholder for more precise specification in future, this level includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.	Transplantation or circulatory support may not currently be indicated.
Modifiers for profiles	Possible profiles to modify
TCS-Temporary Circulatory Support	1, 2, 3 in hospital
A-Arrhythmia can modify any profile. Recurrent ventricular tachyarrhythmias frequent ICD shocks or requirement for external defibrillator, usually more than twice weekly.	Any profile.
FF-Frequent Flyer designating a patient requiring frequent emergency visits or hospitalizations for diuretics, ultrafiltration, or temporary intravenous vasoactive therapy.	3 if at home, 4, 5, 6. A Frequent Flyer would rarely be profile 7.

ADL - activities of daily living; ECMO - extracorporeal membrane oxygenation; IABP - intra-aortic balloon pump; ICD - implantable cardioverter-defibrillator; NYHA - New York Heart Association.

contemporary societies, and improved survival after AMI and the more effective prevention of sudden cardiac death.[33,44] Crucial in this population is diastolic dysfunction with an increasing prevalence, currently even higher than systolic dysfunction.[45] The proportion of patients with HFpEF ranges from 22 to 73%, depending on the definition applied, the clinical setting (primary care, hospital clinic, hospital admission), age and sex of the

studied population, previous myocardial infarction and the year of publication.[41,42,46-56] Men are more likely to develop HF. The lifetime risk of developing HF at the age of 55 years is 33% for men and 28% for women.[40]

The majority of hospitalizations due to AHF reflect the worsening of chronic HF, whereas the remaining 15-20% is HF de novo.[12,57] The mean age is 75 years and over 50% of patients are women.[57] In patients admitted due to AHF, a history of ischaemic heart disease is present in 60%, hypertension in 70%, diabetes mellitus in 40%, atrial fibrillation in 30%, and moderate to severe renal impairment in 20% to 30%.[58] At presentation, approximately 25% of patients are hypertensive (systolic blood pressure [SBP] >160 mm Hg) and only <10% are hypotensive.[59-61] Systolic function is preserved in approximately 50% of AHF patients.[59,62-65] Patients with AHF and HFpEF are more likely to be women, of higher age, with the history of hypertension (severe) and atrial arrhythmias.[62,63,65]

Based on the ESC-HF Pilot Registry European in-hospital patients are generally older than ambulatory patients with chronic HF and more often of female gender.[2] More than half of the patients with AHF have an ischaemic aetiology, but this is confirmed by coronary angiography only in 64% of the cases.[2] There are relevant differences across the different areas in Europe with respect to demographic and clinical characteristics as well as for pharmacological treatments and devices used. Hospitalized patients from Eastern countries are younger, with more commonly an ischaemic aetiology, with a higher systolic blood pressure, and are more frequently treated with blockers of the renin-angiotensin-aldosterone system.[2] Similar findings are seen for ambulatory patients, but with a better adherence to current treatment guidelines.[2] An increase in prescriptions of life saving therapies in HF patients has been demonstrated over recent years.[66]

Despite significant advances in the diagnosis and treatment of HF over recent decades, HF patients still have a poor long-term prognosis [3,34] with high rates of recurrent HF hospitalizations accompanied, however, by only slightly lower mortality rates.[34] Hospitalizations due to HF are ominous, because more than one-third of patients so affected will be re-hospitalized or will die within 90 days of discharge.[61]

The cumulative total mortality rate in the ESC-HF Pilot Registry at 1-year follow-up was 17.4% in patients with AHF, while all-cause mortality at 1 year for ambulatory patients was 7.2%.[2] In patients with HFrEF all-cause mortality was higher than in patients with HFpEF, respectively 18.6% and 13.4% at the 1-year follow-up.[2] In ESC-HF Pilot Registry, the readmission rate (at least once) is >40% during the 1-year follow-up.[2]

Declarations of interest

The authors declare no conflict of interest.

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