Advanced heart failure: A review

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Abstract

Heart failure (HF) has been recognized as a pandemic and is a serious clinical and health problem associated with significant mortality, morbidity and expenditure on healthcare, especially among older people. Progress in medicine has made it possible for an increasing number of people with HF to live longer than ever before. Therefore, a new and serious clinical problem has appeared – advanced heart failure (AHF). A better understanding of this issue is very important, because there are many more patients waiting for transplantations than there are available hearts. The role of the medical team is to keep the patient in the best condition until the heart transplant/implantation of left ventricular assist devices or at least to ensure the best possible quality of life. This article reviews the available data on AHF. The authors have succinctly presented different definitions and methods of the AHF diagnosis established by medical societies, as well as epidemiological data, methods of assessment, and possible treatment strategies.

Key words: heart failure, advanced heart failure, stage D, decompensation

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Definition of advanced heart failure

According to the European Society of Cardiology, the term “advanced heart failure” (AHF) was used to characterize patients with severe symptoms, recurrent decompensation and severe cardiac dysfunction.¹ There is no single condition that defines AHF; however, there is a pattern of clinical characteristics that may suggest that the patient suffers from it.² The newest definition describes AHF as a stage of heart failure (HF) where the conventional treatment (the optimal medical, surgical and device therapy) is insufficient to control the symptoms. Moreover, advanced therapies (e.g., cardiac transplantation and mechanical circulatory support) or palliative therapies are needed. Advanced HF patients remain severely symptomatic, despite the optimal guideline-directed management, regardless of left ventricular ejection fraction (LVEF). Ambulatory patients of class IV according to the New York Heart Association (NYHA) may also be included.³ This type of HF is often described as refractory or stage D according to the American Heart Association (AHA).⁴

Different diagnostic criteria

It is difficult to clearly define AHF. Different approaches of cardiac societies to this issue are summarized in Table 1

Table 2. The differences between stage C and stage D advanced heart failure (AHF) in comparison to the functional capabilities of patients (the New York Heart Association (NYHA) class)

ACCF/AHA stages of HF		NYHA functional classification	
C	Structural heart disease with prior or current symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause the symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in the symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes the symptoms of HF.
		IV	Unable to carry on any physical activity without the symptoms of HF, or the symptoms of HF at rest.
D	Refractory HF requiring specialized interventions.	IV	Unable to carry on any physical activity without the symptoms of HF, or the symptoms of HF at rest.

and Table 2. The NYHA classification of patients seems to be insufficient to optimally determine which patients qualify for particular available medical and pacing therapies, cardiac transplantation or mechanical circulatory support. Patients requiring the latter should be classified using the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) profiles.⁶

Table 1. Different diagnostic criteria of advanced heart failure (AHF)

European Society of Cardiology (ESC) ³	American College of Cardiology Foundation/ American Heart Association (ACCF/AHA) ^{4,5}
<p>All the following criteria must be present, despite the optimal guideline-directed treatment:</p> <ol style="list-style-type: none"> 1. Severe and persistent symptoms of HF (NYHA class III (advanced) or IV). 2. Severe cardiac dysfunction defined by a reduced LVEF ($\leq 30\%$), isolated RV failure or non-operable severe valve abnormalities, or congenital abnormalities, or persistently high (or increasing) BNP or NT-proBNP values and data of severe diastolic dysfunction, or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF. 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 inability to exercise or low 6MWT (<300 m) or pVO_2 (<12–14 mL/kg/min), estimated to be of cardiac origin. <p>In addition to the above, extra-cardiac organ dysfunction due to heart failure (e.g., cardiac cachexia, liver or kidney dysfunction) or type 2 pulmonary hypertension may be present, but are not required.</p> <p>Criteria 1 and 4 can be met in patients who have cardiac dysfunction (as described in criterion 2), but who also have substantial limitation due to other conditions (e.g., severe pulmonary disease, non-cardiac cirrhosis, or – most commonly – by renal disease with mixed etiology). These patients still have limited quality of life and survival due to advanced disease and warrant the same intensity of evaluation as someone in whom the only disease is cardiac, but the therapeutic options for these patients are usually more limited.</p>	<ul style="list-style-type: none"> – Repeated (≥ 2) hospitalizations or emergency department visits for HF in the past year. – Progressive deterioration in renal function (e.g., rise in BUN and creatinine). – Weight loss without other cause (e.g., cardiac cachexia). – Intolerance to ACEI due to hypotension and/or worsening renal function. – Intolerance to β-blockers due to worsening HF or hypotension. – Frequent systolic blood pressure <90 mm Hg. – Persistent dyspnea with dressing or bathing requiring rest. – Inability to walk 1 block on the level ground due to dyspnea or fatigue. – Recent need to escalate diuretics to maintain the volume status, often reaching daily furosemide equivalent doses over 160 mg/day and/or the use of supplemental metolazone therapy. – Progressive decline in serum sodium, usually to <133 mEq/L. – Frequent implantable cardioverter defibrillator shocks.

ACEI – angiotensin-converting enzyme inhibitor; BNP – brain natriuretic peptide; BUN – blood urea nitrogen; HF – heart failure; HFmrEF – HF with mid-range ejection fraction; HFpEF – HF with preserved ejection fraction; LV – left ventricle; LVEF – left ventricular ejection fraction; NT-proBNP – N-terminal portion of proBNP; NYHA – the New York Heart Association; pVO_2 – peak oxygen consumption; RV – right ventricle; 6MWT – 6-minute walk test distance.

Epidemiology and mortality

Heart failure is a global pandemic and continues to increase in prevalence. At least 26 million people worldwide are affected.⁷ Patients with AHF comprise an estimated 1–10% of the overall HF population and the prevalence is increasing due to better treatment and survival.³ Data from Olmstead County, USA, suggests that <1% of patients suffer from stage D HF and are subject to exceptionally high mortality.^{5,8} According to the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, patients in stage D who were treated medically experienced 75% mortality at 1 year and no survival at 2 years.^{5,9} Another trial concerning optimally treated patients – the Investigation of Non-Transplant-Eligible Patients Who Are Inotrope Dependent (IN-TREPID) – had survival rates of 22% at 6 months and 11% at 1 year.^{5,10} In a random population-based sample from Olmstead County, stage D HF was associated with only a 20% 5-year survival.^{5,8} The poorest survival, 6% at 1 year, concerns patients who are moving on to end-of-life care on continuous inotropes.^{5,10} Moreover, the mortality risk increases with each subsequent HF hospitalization and low blood pressure.^{2,11–14} While AHF can occur in patients suffering from HF with both preserved and reduced LVEF, a drop in ejection fraction or a very low ejection fraction (≤ 25 –30%) has been associated with a worse prognosis. Right ventricular dysfunction is associated with an adverse prognosis regardless of ejection fraction.² Advanced HF is also associated with poor quality of life for patients.¹⁵

Clinical manifestations

The signs and symptoms of AHF vary; however, certain clinical manifestations may indicate stage D HF, especially with synchronous presentation. It is important to emphasize that these signs and symptoms listed below occur in the optimal therapy, including the insertion of all appropriate devices (e.g., cardiac resynchronization therapy – CRT) and with all reversible causes of HF addressed. The most common clinical manifestations are²:

- dyspnea;
- fatigue;
- exercise intolerance – which also includes the inability to perform activities of daily living, such as bathing or dressing;
- unintentional weight loss – which sometimes leads to cachexia, associated with the loss of muscle and fat, despite proper caloric intake due to catabolic/anabolic imbalances;
- refractory volume overload – despite escalating doses of diuretics (furosemide ≥ 160 mg/day) or frequent use of metolazone; clinically it may be visible as pulmonary congestion, peripheral edema and elevated jugular pressure;

- worsening renal function – despite high doses of diuretics, inadequate diuresis may be presented;
- hypotension and the signs of inadequate perfusion; moreover, the need to cut back the doses of angiotensin-converting-enzyme inhibitors (ACEI) and β -blockers due to symptomatic hypotension suggests AHF^{2,15,16};
- congestive hepatopathy – especially due to right-sided HF, which is often accompanied by left-sided HF;
- refractory arrhythmias – with or without device shocks.

Advanced HF usually occurs as an evolution and progression of HF, but it can also be developed acutely, e.g., after acute myocarditis. There are 2 basic pathophysiologic myocardial mechanisms that cause reduced cardiac output and HF: systolic and diastolic dysfunction.¹⁷ The causes of each dysfunction are variable and should be diagnosed.

Useful prognostic indicators are outlined below (Adapted from Metra et al.¹⁸).

Prognostic determinants of poor outcome in patients with advanced heart failure

- Demographic:
 - advanced age;
 - male gender.
- Clinical:
 - frequent rehospitalizations;
 - advanced NYHA class;
 - intolerance to neurohormonal antagonists;
 - persistent/relapsing signs of pulmonary or peripheral congestion;
 - hypotension;
 - co-morbidities (diabetes, renal failure, hepatic failure, anemia, chronic obstructive pulmonary disease, hyperthyroidism or hypothyroidism, etc.).
- Electrocardiography:
 - resting tachycardia;
 - wide QRS complex.
- Laboratory:
 - hyponatremia;
 - renal insufficiency (blood urea nitrogen (BUN)/serum creatinine);
 - anemia (hemoglobin < 8 mg/dL);
 - hepatic insufficiency;
 - neurohormones (e.g., norepinephrine, endothelin);
 - natriuretic peptides;
 - cardiac myocyte necrosis markers (troponins);
 - inflammatory markers (e.g., C-reactive protein).
- Doppler-echocardiography and right heart catheterization:
 - low LVEF/increased left ventricular end-systolic volume index;
 - decreased left ventricular long-axis systolic shortening;
 - mitral regurgitation/increased left atrial volume;

- signs of increased LV filling pressure;
- low right ventricular ejection fraction (RVEF);
- increased pulmonary vascular resistance.
- Functional capacity:
 - inability to perform an exercise test;
 - increased ventilatory response to exercise (the minute ventilation and CO₂ production ratio (VE/CO₂) slope);
 - low peak oxygen consumption (pVO₂) [mL/kg/min];
 - low 6-minute walk test distance (6MWTd).

Diagnosis

There are no particular tests which can confirm the presence of AHF. As a result, there is a need to perform several diagnostic procedures in order to diagnose AHF and exclude other diseases with similar symptoms. Such procedures include:

- blood tests:
 - complete blood count,
 - electrolytes – AHF is a cause of hyponatremia,
 - renal function test: BUN, creatinine, glomerular filtration rate – abnormalities might be visible due to the worsening of renal function,
 - liver function test: alanine aminotransferase, aspartate aminotransferase, bilirubin – abnormalities due to congestive hepatopathy,
 - elevated levels of brain natriuretic peptide (BNP) or N-terminal portion of proBNP (NT-proBNP) are usually present;
- chest X-ray – used to detect pulmonary edema, pleural effusions, pulmonary vascular congestion, and other episodes of fluid retention;
- electrocardiogram (ECG) – useful in the detection of atrial fibrillation, which is more common in patients with AHF; ventricular arrhythmias may also occur¹⁹;
- exercise testing, e.g., 6MWTd (≤ 300 m) and/or cardiopulmonary exercise testing;
- echocardiography – a complete transthoracic echocardiogram should be performed in all patients suspected of having AHF to assess the changes in biventricular and valvular function that may be contributing to the worsening of the symptoms;
- right heart catheterization – required in patients undergoing evaluation for mechanical circulatory support and cardiac transplantation.²

Differential diagnosis

The exclusion of other, often reversible, pathologies is vital before making a final diagnosis of AHF. Conditions that most commonly imitate the signs and symptoms of AHF include:

- underlying kidney disease, which causes the worsening of renal function;

- cardiorenal syndrome;
- lung disease (especially chronic obstructive pulmonary disease, present in up to 40% of patients) as a cause of dyspnea²;
- liver disease, such as cirrhosis, which may evoke the symptoms of retention of fluid (including ascites, edema of lower extremities and fatigue);
- non-optimal therapy.

Furthermore, it is necessary to search for reversible causes of HF, such as tachyarrhythmias, inflammatory diseases, endocrine disorders (e.g., hyperthyroidism), as well as cardiomyopathies: peripartum, Takotsubo or induced by drugs and alcohol. Any reversible reason of cardiomyopathy should be considered as a potential causative and curable factor of AHF. Arrhythmias associated with arrhythmogenic cardiomyopathy include long-standing atrial fibrillation, atrial flutter, atrial tachycardia, reentrant supraventricular tachycardia, accessory pathway tachycardia, frequent ectopic beats, and ventricular tachycardia. The optimal rhythm control or even the restoration of the sinus rhythm is crucial in this case.²⁰

Moreover, patients with HF often suffer from malnutrition and that also might be the cause of symptoms similar to those presented in AHF. It is also important to differentiate end-stage HF, which is always irreversible, from AHF, which, by contrast, might be reversible to some extent.

Treatment

- Medical treatment:
 - Angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers (ARB) in case of intolerance of ACEI.
 - β -blockers.
 - Mineralocorticoid antagonists. According to the ESC guidelines concerning AHF, the combination of 3 neurohormonal antagonists should be attempted in all patients with advanced chronic HF. All patients should receive an ACEI and a β -blocker unless there is intolerance. Either an ARB (e.g., candesartan) or mineralocorticoid antagonist (e.g., spironolactone) should then be added.¹⁸
 - Diuretics – usually high doses are necessary. When used intravenously, continuous infusion of loop diuretics is more efficient than the bolus therapy.¹⁸ The combination of thiazide or spironolactone with loop diuretics has been proposed to overcome the diuretic resistance, commonly present in patients with AHF.^{4,18}
 - Nitrates – used to relieve concomitant angina, but the long-term effects are visible only in conjunction with hydralazine in black patients according to African-American Heart Failure Trial.^{18,21}
 - Digoxin – used in patients with concomitant atrial fibrillation.
 - Anti-platelet and anti-thrombotic agents – used in patients with atrial fibrillation, unless contraindicated.

- Continuous infusion of inotropes – can be used to improve end-of-life quality, but it is vital to be attentive to the adverse effects of catecholamines (e.g., excessively high heart rate), which can cause the worsening of cardiac function.
- Ivabradine – appears to be a promising approach. It is well tolerated, effectively reduces heart rate, increases stroke volume and preserves cardiac output.²²
- New drugs: sacubitril/valsartan – a representative of a new group of drugs (angiotensine-receptor-neprilysin inhibitors – ARNI), recommended to be used instead of ACEI/ARB (spectacular results of the PARADIGM-HF trial) and levosimendan – a calcium sensitizer and inodilator, which increases the force of contraction, decreases preload and afterload, and also exerts some cardioprotective effect (in acutely decompensated congestive HF and, according to the LION-HEART study, in advanced HF).^{23–25}
- Cardiac resynchronization therapy.
- Implantable cardioverter defibrillator (ICD) – however not in NYHA IV class, unless the patient is under consideration for CRT implantation, left ventricular assist devices therapy or heart transplantation.
- Surgical strategies:
 - Heart transplantation – the treatment of choice for patients without contraindications.³
 - Mechanical support – implantable ventricular assist devices might be used as a bridge to recovery or heart transplantation, or as a destination therapy (the last indication is not approved in Poland).
- Palliative medicine/hospice care – at the terminal stadium of the disease.

The treatment of patients with a coexistence of AHF and atrial fibrillation is especially difficult due to limited therapeutic options and a higher risk of bleeding (high prevalence of renal and liver failure). The His-bundle-pacing-based ICD may be an innovative approach in decompensated chronic HF and concomitant permanent atrial fibrillation.²⁶

Summary

Although AHF is a common worldwide problem, there are many questions that remain unanswered. Many prognostic indicators are still unknown and there are no randomized controlled trials of novel pharmacologic and device interventions. Nevertheless, some medical societies pin their hopes on Entresto™, although its use in AHF is not supported by guidelines. Furthermore, in our clinical practice concerning AHF, we very often struggle with significant ethical dilemmas that should be always solved in cooperation with a patient. We need to ask if our patient wants aggressive treatment or resuscitation in case of a sudden cardiac arrest. We must know if the quality of life is for the patient more important than living as long as possible. Answers to these questions are vital in making

proper medical decisions and allow us to provide appropriate and sustainable treatment for the patient, which should be always the main goal for any medical team.

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