Review Article

I NEED HELP: How to Indentify Patients with Advanced Cardiac Dysfunction?

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Abstract

Heart failure (HF) is a clinical syndrome characterized by inadequate tissue oxygen supply. In spite of the best current approach to heart diseases, population aging in individuals with heart disease has resulted in increased incidence of HF.

In Brazil, HF represents the second leading cause of hospitalization due to cardiovascular diseases, and it has high mortality in its most advanced stage. The difficult recognition of therapeutic refractoriness can often lead to delays in referral to specialized centers that are able to promote reduced symptoms, improved quality of life, and increased survival.

Therapeutic options are limited in advanced HF, and heart transplantation is the therapy of choice. Organ availability is a major limitation, making circulatory support an increasingly present reality, with improved results.

Definition

The term advanced heart failure (HF) encompasses the group of patients with chronic HF who evolve with progressive worsening of cardiac function and symptoms. Ultimately, these patients progress to refractoriness to standard treatment guided by the current guidelines. Thee patients' prognosis is limited, with mortality reaching 25% to 75% in one year. Accordingly, in order to guarantee favorable outcomes, they require advanced therapies, such as heart transplantation, support with a mechanical circulatory assist device, and/or palliative care.[1]

Numerous classification systems have been created to characterize patients with HF and to select advanced cases. The assessment of functional class proposed by the New York Heart Association (NYHA) defines individuals with symptoms at rest or during any physical activity as class IV. In 2001, the American College of Cardiology (ACC) and the American Heart Association (AHA) described stage D patients as those requiring specialized interventions due to the presence of refractory symptoms despite optimal medical therapy. The Interagency Registry for Mechanically Assisted Circulation (INTERMACS) classification was developed to stratify the risk of patients with advanced HF and to establish prognosis and urgency of intervention. Table 1 shows the classification systems together.[2]

The definition of advanced HF has evolved over the past decades. The Heart Failure Association of the European Society of Cardiology (HFA-ESC) update from 2007 to the 2018 document introduced a new concept for classifying these patients. Although left ventricular ejection fraction (EF) is frequently reduced, it is not a mandatory criterion for the diagnosis of advanced HF, given that it can develop in patients with HF with preserved ejection fraction (HFpEF) as well. Extracardiac organ dysfunction due to HF (for example, cardiac cachexia, kidney dysfunction, and liver dysfunction) or pulmonary hypertension may be present, but they are not required for definition of advanced HF. The updated HFA-ESC 2018 criteria are displayed in Table 2.[3]

HF risk scores were developed from specific cohorts, including the group of patients with acute HF, HF with reduced EF, and/or HFpEF. They are important tools in clinical decision-making, to the extent that they accurately assist in adaptation and identification of the need for disease-modifying treatments, advanced therapies, or the indication of end-of-life care. It has been observed that they are still underused in clinical practice and that their results should not be analyzed in an isolated manner.[4]

There are different risk scores for HF, including Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM),[5] Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure (GISSI-HF),[6] Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC), and Seattle Heart Failure Model (SHFM).[7] MAGGIC seems to have the best discriminatory power for one-year mortality.[4]

Incidence

It is estimated that approximately 64.3 million people worldwide are living with HF, approximately 1% to 2% of the adult population in developed countries,[8] and the disease has been characterized as a global pandemic. Over the decades, great difficulty has been observed in establishing HF criteria that are easy to reproduce, followed by the challenge of obtaining reliable data in some regions of the world.

Keywords

Heart Failure; Heart Transplantation; Classification

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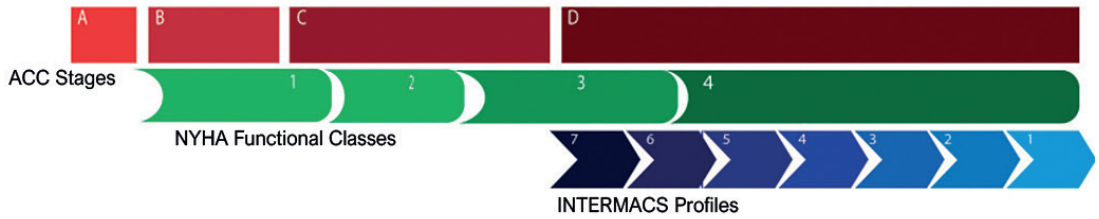
Table 1 – Stages and symptoms of heart failure in different classification systems



ACC stages	NYHA functional classes	INTERMACS profiles
A: Patients at risk of developing heart failure, without functional or structural heart disease	**I:** No limitation of routine physical activity	**I:** Severe cardiogenic shock
B: Structural heart disease, without symptoms of heart failure	**II:** Mild symptoms during routine physical activity	**II:** Progressive decline despite inotrope use
C: Structural heart disease. Prior or current symptoms of heart failure	**III:** Symptoms during less than ordinary physical activities. Important limitation. Comfortable only at rest.	**III:** Stable, but inotrope dependent
D: Heart failure refractory to clinical treatment, requiring specialized intervention in heart failure centers	**IV:** Severe limitation to any physical activity without discomfort. Symptoms at rest.	**IV:** Frequent hospitalizations
		V: Housebound, exertion intolerant
		VI: Exertion limitation
		VII: NYHA III

Adapted from Truby LK, Rogers JG[2] Stages of heart failure as described by the American College of Cardiology (ACC), New York Heart Association (NYHA) functional classes, and the Interagency Registry for Mechanically Assisted Circulation (INTERMACS).

Table 2 – Criteria for defining advanced heart failure

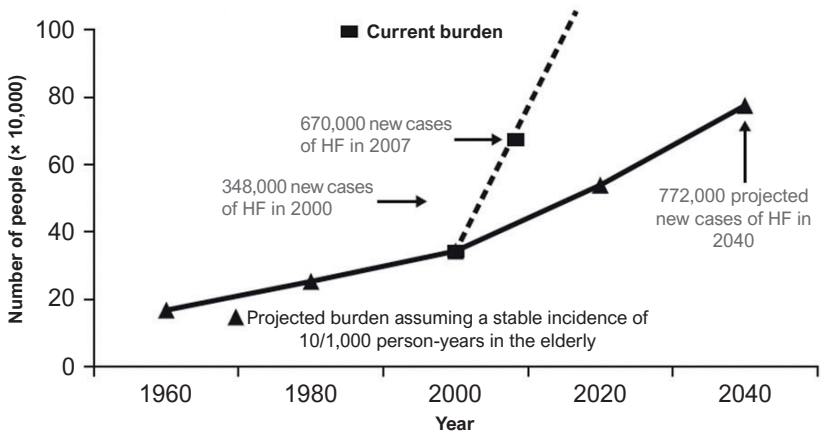
1.	Severe and persistent symptoms of HF (NYHA III or IV).
2.	Severe ventricular dysfunction defined by at least one of the following: • LVEF ≤ 30% • Isolated right HF • Non-operable severe valve abnormalities • Non-operable severe congenital abnormalities • Persistently high BNP or NT-proBNP values and data showing severe diastolic dysfunction or LV structural abnormalities, according to the definition criteria for HFpEF
3.	Episodes of pulmonary or systemic congestion requiring high doses of intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing more than 1 unplanned visit to the emergency department or hospitalization within the past 12 months
4.	Severe impairment of exercise capacity, with inability to exercise or low 6MWTD (< 300 m) or pVO_2 (< 12 to 14 ml/kg/min), estimated to be of cardiac origin

Adapted from Metra et al.[1] 6MWTD: 6-minute walk test distance; BNP: B-type natriuretic peptide; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; LV: left ventricle; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; pVO_2: peak exercise oxygen consumption.

It is historically predominant in male individuals,[9] but the recent inclusion of HFpEF and HF with mildly reduced EF has statistically increased the representation of women in this syndrome.[3] Incidence is lower in young people, around 3 to 5 per 1,000 inhabitants in Europe, and it increases substantially in those over 70 years of age.[10]

Several models have shown acceleration in new cases of HF from the turn of the millennium, with nearly 915,000 new cases in the United States in 2016[11] (Figure 1). This greater number of new patients is added to those with prolonged survival due to the best medical and invasive treatment, in addition to the global increase in life expectancy, thus corroborating a substantial increase in the prevalence of the disease.

In Brazil, there are few multi-center analyses of the situation of HF; however, a group from Paraíba[12] managed to



The annual incidence of heart failure (HF) reported in the United States (squares and dotted line) exceeds the projected annual incidence (triangles and solid line), calculated based on a stable incidence of 10/1,000 person-years in the elderly. Source: Lam et al, 2011. Reproduced with permission, John Wiley & Sons.

Figure 1 – *Burden of heart failure*

demonstrate a reduction in the national mortality rate. It is, however, worth noting, that there is an increase in hospital mortality rates and hospitalization time, indicating a lack of appropriate treatment for the most severe disease forms.

Measurement of individuals with advanced HF is even more complex than that of HF *lato sensu*, and it is subject to variations in the definition criteria, with scores that are not very accurate; nevertheless, the ADHERE registry[13] found, in the mid-2000s, that 5% of hospitalizations were related to advanced HF. These data seem to underestimate these patients with severe HF, given that, in 2019 in the United States, more than 3,000 patients were treated with a left ventricular assist devices; around 3,000 patients received heart transplants, and an additional 3,500 patients were waiting in line to receive an organ.[2]

How to Identify It

HF has a challenging clinical course that poses difficulties even to experienced clinicians, seeing that it is a chronic disease whose evolution can be subtle over time, giving patients and healthcare staff a false sense of clinical stability.

Unlike other chronic diseases, HF may have a fluctuating survival curve with clinical improvement after a severe episode of decompensation and subsequent reestablishment of functional class. These individuals can, with the support of optimal medical therapy, still have reasonable survival. Others will maintain worsening of symptoms and high mortality in a short timeframe. The limit between these two scenarios is tenuous and imprecise, making it of the utmost importance to develop warning signs in advanced HF. (Figure 2)

The addition of biomarkers, arrhythmic load, exercise performance, and EF evolution bring greater objectivity when establishing the best moment for referral; however, there is no consensus among the leading societies as to what these markers should be. In spite of this, advanced NYHA functional class (III/IV), optimized drug therapy, and episodes of decompensation requiring hospitalization are unanimously recognized as markers of worse prognosis.[2]

A useful mnemonic that can help identify patients who require referral to centers specializing in HF treatment is "I NEED HELP". It integrates aspects related to clinical history, hospitalizations, drug intolerance, EF, symptoms, and end-organ dysfunction (Table 3).[14]

The factors listed in this mnemonic device are not the only ones of concern, but, in multivariate analyses of several clinical trials, they were shown to be important predictors, and the presence of any one of these factors indicates that the opinion of a referral center should be sought.

EF is an important variable. In patients with HF with reduced EF, for every 10% reduction in EF, a significant increase occurs in events related to sudden death and death due to HF.[15] However, difficulties are often observed in the risk stratification of patients with preserved EF. Patients in this population are equally severe when they have other warning signs, and their diagnosis ends up being delayed, with the addition of a limited therapeutic arsenal.

The NYHA classification is one of the most widely used to describe the severity of symptoms. It allows clinical evaluation, helps in therapeutic management, and also has an excellent prognostic ratio. However, there are limitations, as it depends on self-reported symptoms, which are influenced by each patient's subjectivity. In these individuals, the use of the cardiopulmonary exercise test (CPET) provides more accurate information, highlighting warning signs even in asymptomatic individuals, and it is a great instrument for calibrating risk and providing prognosis

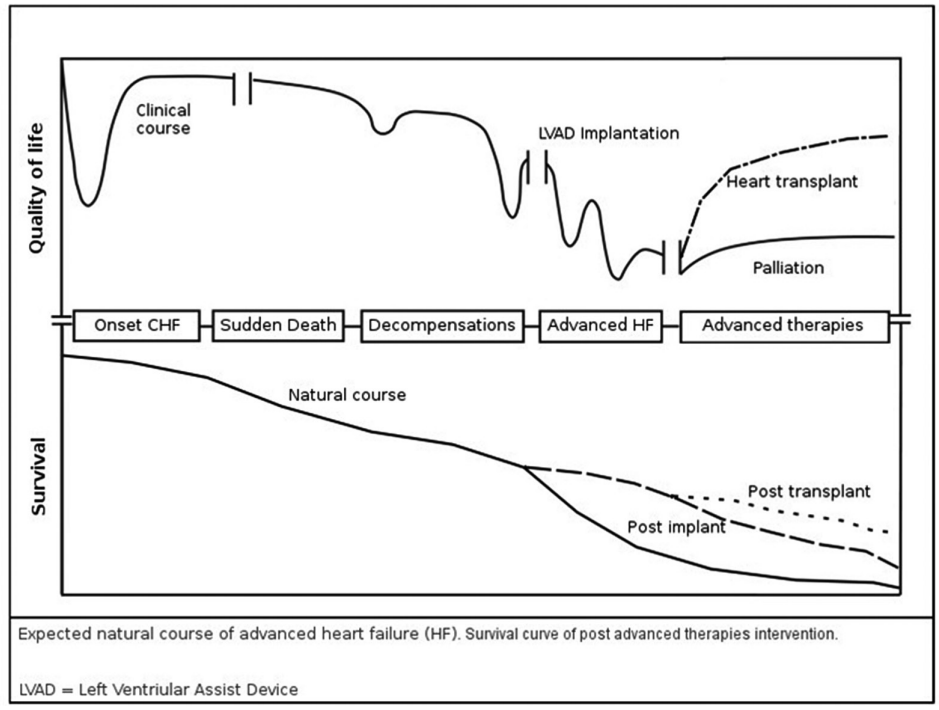


Figure 2 – *Clinical Course of Advanced HF.*

Table 3 – "I NEED HELP" mnemonic for identifying patients with advanced heart failure

I	Inotrope dependent/intolerant to optimized therapy
N	Persistent NYHA III/IV
E	Ejection fraction below 20%
E	Persistent edema, refractory to progressive doses of diuretics
D	Defibrillator (recurring appropriate shock)
H	Recurring hospitalizations and emergency department visits in the last 12 months
E	Persistent elevation in natriuretic peptides
L	End-organ damage
P	Systolic blood pressure persistently below 90 mmHg

NYHA: New York Heart Association.

for individuals with advanced HF. In patients with HFpEF and HF with mildly reduced ejection fraction, CPET also maintained accuracy, with excellent correlation of peak VO_2 and ventilatory response (VE/VCO_2 slope).[16]

B-type natriuretic peptide (BNP) is a biomarker with great prognostic utility. A persistent elevation in BNP indicates risk of events and mortality. In a systematic review that analyzed 19 studies, for every 100 pg/mL increase in plasma BNP, a 35% increase was observed in the relative risk of death.[17]

Inotropic therapy, taken alone, is a marker of in-hospital death,[18] and it should be used exclusively in patients in shock; therefore, patients who required inotropic therapy coming from a hospitalization should have priority in post-discharge reassessment.

Another even more challenging scenario of refractoriness is that of patients with cardiogenic shock (CC), who may have an acute presentation (first-time diagnosis) or have a chronic disease that has evolved with low output and perfusion deficit. In these cases, temporary inotropic and/or mechanical support are fundamental until etiological diagnosis has been made and prognosis established. To this end, a shock team with protocols for fast and accurate action is essential to avoid multiple organ failure.[19]

In order to improve recognition and agility in interventions in CC, the Society for Cardiovascular

Angiography and Interventions (SCAI) proposed a new classification in 2019 (Figure 3), subdividing CC into five stages, with a focus on tissue perfusion and signs of dysfunction organic. Stage A patients at risk for shock, and stage B represents beginning of shock. Identification of and action upon these stages improve prognosis and have an impact on survival.[20]

Another important point is hemodynamic monitoring with a pulmonary artery catheter, which becomes fundamental in the diagnosis of CC, bringing more therapeutic precision. Recently, the Cardiogenic Shock Working Group (CSWG) evaluated invasive monitoring in 1,414 patients with CC, showing that guided therapy reduced mortality in this population.[21]

Around the world, treatment centers for advanced HF indicate that patients receive late referral. Multiple strategies are needed to improve the recognition and care for these patients in both the acute and chronic phases, thus allowing the use of advanced therapies.

Management of advanced HF

As previously indicated, patients with advanced HF present high complexity and elevated mortality; for this reason, they should be followed up in specialized HF centers.[14,22] These centers aim to rule out reversible causes of HF and guarantee the use of all possible medical therapies, including resynchronization therapy and valve management, when applicable, in addition to critical multidisciplinary support in order to identify eligibility for more advanced therapies.

In this stage, patients show signs of clinical refractoriness to optimized medical and non-medical treatments recommended by national and international guidelines.[3,14,22] Previously well-tolerated disease-modifying medications may require dose reduction or even suspension. Different degrees of tissue hypoperfusion may determine the association of inotropes. The progressive deterioration of renal function may require a combination of diuretics, intravenous diuretic therapy, or even renal replacement therapy.[2,3,14,22]

As a therapeutic plan for advanced HF, HF centers basically have three available options:

1. Heart transplantation: Heart transplantation is the treatment of choice in the absence of contraindications (Table 4). The number of heart transplantations is growing, with more than 5,000 procedures performed worldwide each year. Brazil has also managed to increase the number of cases in recent years with 380 transplants in 2017, but this is still below the population's need, which is estimated to be 1,649 transplants/year.[23] A major limiting factor is organ availability, leading to the option of circulatory assistance devices for selected cases.

2. Circulatory assist devices: These devices promote symptomatic improvement and allow satisfactory survival when compared to the results of heart transplantation. They are interesting options in some cases where heart transplantation is contraindicated (target therapy), and they can be used as a "bridge to heart transplantation" or as a "bridge to recovery".[2,3,14,22]

Today, there is a wide range of different types of circulatory assist devices available. The choice of device will depend on the therapeutic goals, the patient's severity or degree of hemodynamic instability, the team's skills in dealing with different support methods, and the availability of the methods at each institution.[22]

Devices are classified by manufacturers according to the support time expected for the method, as follows:

- Short-term circulatory assist devices: intra-aortic balloon pump, Impella®, and extracorporeal membrane oxygenation;
- Medium-term circulatory assist devices: Centrimag®;
- Long-term circulatory assist devices: Heart Mate III®.[22,23]

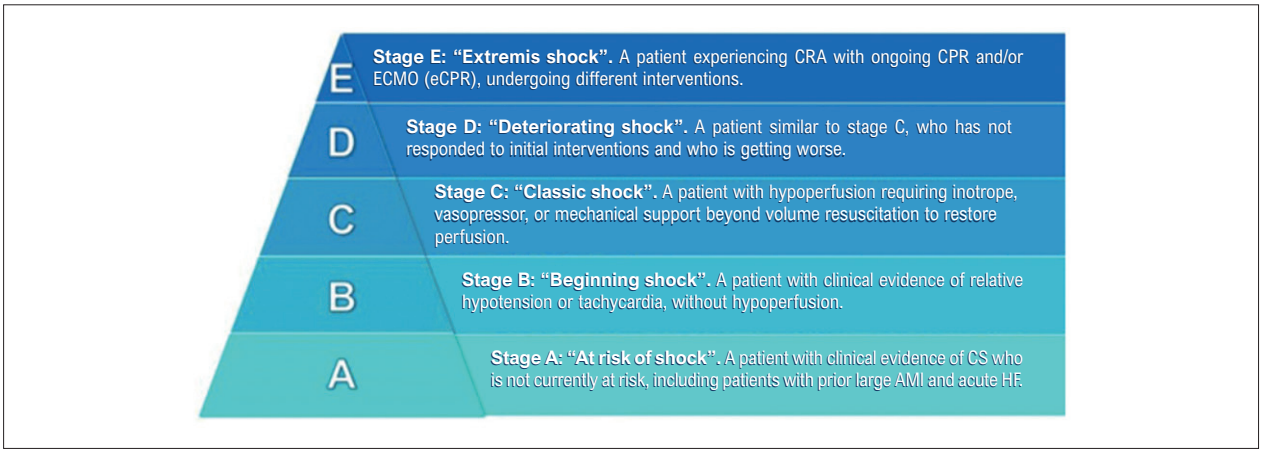


Figure 3 – *Classification of the Society for Cardiovascular Angiography and Interventions (SCAI) for cardiogenic shock. Adapted from: Baran DA et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock. Catheter Cardiovasc Interv. 2019; 94(1): 29-37. AMI: acute myocardial infarction; CRA: cardiorespiratory arrest; CPR: cardiopulmonary resuscitation; CS: cardiogenic shock; ECMO: extracorporeal membrane oxygenation; HF: heart failure.*[20]

The INTERMACS classification proposed in 2011 allows prognostic assessment and specifies the urgency for indication and implantation of circulatory assist devices in advanced HF. For the most severe and unstable patients (INTERMACS 1) implantation of circulatory assist devices is recommended within hours. In these cases, due to the high mortality and complexity, short-term methods are suggested, preferably with peripheral and rapid implantation. For patients in INTERMACS 2, implantation of short- or medium-term devices can be considered. For patients classified as INTERMACS 3 (stable, using inotropes) implantation of medium-term devices is recommended. Patients with INTERMACS classification greater than 4 can be assessed for elective implantation of long-term devices (Table 5).[2,3,14,22,24,25]

3. Palliative care: This option is for patients for whom heart transplantation and circulatory assist devices are not indicated or available. This form of care is ideally performed by specialists focused on quality of life and symptomatic control. Indications for devices such as pacemakers and defibrillators are reassessed. Palliative care is able to minimize rehospitalizations and humanize treatment in HF.[2,3,14,22]

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Author Contributions

Conception and design of the research: Miranda JSS; Acquisition of data: Miranda JSS, Fatorelli A, Salles V; Analysis and interpretation of the data: Salles V; Writing

Table 4 – Indications and contraindications for heart transplantation

Indications (Class I)	Possible contraindications
– Advanced HF with dependence on inotropic drugs and/or mechanical circulatory support – Advanced HF with persistent NYHA functional class IV in spite of optimal treatment, in the presence of other poor prognostic factors – Advanced HF with peak VO2 lower than or equal to 12 ml/kg/min while using beta-blocker or lower than or equal to 14 ml/kg/min in patients intolerant to beta-blockers	– Over 70 years of age – Active drug use, tobacco use, alcoholism – Uncontrolled psychiatric disorders, dementia syndromes or severe mental retardation, comatose states – Neoplasms without cure criteria – Non-adherence to proposed therapy before heart transplantation – Coexistence of comorbidities that limit the patient's life to less than 1 year – Fixed pulmonary hypertension;

HF: heart failure; NYHA: New York Heart Association.

Table 5 – INTERMACS classification[22,25]

Profile	Description	Hemodynamic state	Timeframe for intervention
I	Severe cardiogenic shock	Persistent hypotension, notwithstanding use of inotropres and IABP, associated with organ dysfunction	Hours
II	Progressive decline, despite use of inotropes	Deterioration in renal function, liver function, and nutrition and lactatemia, despite optimized doses of inotropic agents	Days
III	Stable, but inotrope dependent	Clinical stability under inotrope therapy, but with a history of failure to wean from inotropes	Weeks to months
IV	Frequent hospitalizations	Signs of fluid retention, symptoms at rest, and frequent emergency department visits	Weeks to months
V	Housebound, exertion limitation	Pronounced limitation to activity, comfortable at rest, despite fluid retention	Variable urgency, depending on nutritional state and degree of organ dysfunction
VI	Exertion limitation	Moderate exertion limitation and absence of signs of hypervolemia	Variable urgency, depending on nutritional state and degree of organ dysfunction
VII	NYHA III	Hemodynamic stability and absence of hypervolemia	Not indicated

IABP: intra-aortic balloon pump; NYHA: New York Heart Association.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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