

When to Suspect Advanced Heart Failure in Heart Failure with Preserved Ejection Fraction?

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Advanced heart failure (HF) accounts for almost 15% of patients with HF, and it has been defined as “the presence of progressive and/or persistent severe symptoms despite optimal guideline-directed management regardless of left ventricular ejection fraction (LVEF).”^{1,2} Although patients with advanced HF are thought to usually present with severely reduced LVEF, it should be noted that the definition of advanced HF does not require low LVEF. Indeed, more than half of patients with advanced HF have LVEF above 40%, with all-cause mortality similar to those with LVEF below 40%.² Identifying patients with advanced HF is important in order to refer them to proper management, including heart transplantation, mechanical circulatory support, or palliative care. But when should we suspect advanced HF when the LVEF is preserved?

First, let's look at the current definition criteria for advanced HF (Table 1). Beyond LVEF below 30%, severe cardiac dysfunction includes severe congenital or valve disease or arrhythmogenic right ventricular cardiomyopathy. But these conditions have been excluded from HFpEF definitions in clinical trials and they are not mechanistically generally considered heart failure with preserved ejection fraction (HFpEF).^{3–5} Advanced HFpEF requires the presence of severe diastolic dysfunction or left ventricular (LV) structural abnormalities accompanied by elevated natriuretic peptides.

Diastolic dysfunction is assessed by mitral flow velocities, mitral annular e' velocity, E/e' ratio, peak tricuspid regurgitation jet velocity, and maximum left atrial volume index. Although the American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines provide grading criteria for diastolic dysfunction (grades I to III), there is no consensus on how severe diastolic dysfunction should be specifically defined to fulfill the criteria for advanced HFpEF.⁶ In a recent epidemiological study of advanced HF in Olmsted County, United States, Dunlay et

al defined severe diastolic dysfunction in patients with HF with mildly reduced ejection fraction or HFpEF as diastolic dysfunction grade 2 or greater. They also used other criteria that suggested elevated filling pressures, such as E/e' ratio above 9, to indicate severe diastolic dysfunction, but this was because diastolic dysfunction grading was missing in the administrative data.²

The definition of advanced HF also requires that diastolic dysfunction be accompanied by elevated natriuretic peptides, but it should be kept in mind that patients with advanced HFpEF display lower natriuretic peptide blood levels compared to patients with advanced heart failure with reduced ejection fraction (HFrEF).² Furthermore, comorbidities are more common in patients with HFpEF, and they can contribute to their functional impairment and worsen quality of life, which makes the diagnosis of advanced HFpEF more challenging.²

For the diagnosis of advanced HFpEF, severe symptoms, repeated hospitalizations for HF, and/or severe impairment in functional capacity should persist, despite optimal medical treatment. Differently from HFrEF, therapeutic options for HFpEF are limited. Guideline-based recommendations for treatment of HFpEF include treatment of cardiovascular and non-cardiovascular comorbidities, such as treating myocardial ischemia, reducing blood pressure in hypertension, and controlling heart rate in atrial fibrillation.⁷ The guidelines also recommend using diuretics to alleviate congestion, as well as screening and treating specific etiologies, such as cardiac amyloidosis. An angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker/sacubitril-valsartan, a mineralocorticoid receptor antagonist, and a beta-blocker are not required for HFpEF, but they can be considered if tolerated for patients with LVEF below normal (i.e. HFmrEF) following results from sub-analysis of trials.^{8–12} In addition, after the results of the first positive outcome-driven trial in HFpEF, empagliflozin should be considered as part of optimal treatment in HFpEF.⁵ Patients with advanced HFpEF are those who remain severely symptomatic despite optimal clinical treatment, and they should be considered for advanced therapies.

The rational of advanced therapies in HFpEF relies upon our knowledge on the pathophysiology of the disease and underlying mechanisms of symptom development. HFpEF is characterized by increased LV and left atrial (LA) stiffness, which results in high LA pressure and pulmonary capillary wedge pressure, particularly during exercise. Patients with HFpEF tend to have exercise intolerance in early stages and to develop congestive signs/symptoms with the progression of the disease.¹³

Keywords

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Table 1 – Updated Heart Failure Association-European Society of Cardiology criteria for defining advanced heart failure

All the following criteria despite optimal guideline-directed treatment:

1. Severe and persistent symptoms of HF (NYHA III [advanced] or IV)
2. Severe cardiac dysfunction defined by either:
 - LVEF $\leq 30\%$
 - Isolated RV failure (e.g. ARVC)
 - Non-operable severe valve abnormalities or congenital abnormalities
 - Persistently high BNP or NT-proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the European Society of Cardiology definition of HFpEF or 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 to 14 mL/kg/min), estimated to be of cardiac origin.

In addition to the above, extra-cardiac organ dysfunction due to HF (e.g. cardiac cachexia, liver, or kidney dysfunction) or type 2 pulmonary hypertension may be present, but are not required.

Criteria 1 and 4 can be met in patients who have cardiac dysfunction (as described in criterion number 2), but who also have substantial limitation due to other conditions (for instance, severe pulmonary disease, non-cardiac cirrhosis, or 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 patients in whom the only disease is cardiac, but the therapeutic options for these patients are usually more limited.

ARVC: arrhythmogenic right ventricular cardiomyopathy; BNP: B-type natriuretic peptide; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; LV: left ventricular; 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; RV: right ventricular; 6MWT: 6-minute walk test distance. Source: Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology.¹

The management of congestion can be challenging in patients with advanced HFpEF. Treatment options are similar to those in HFrEF, namely, high doses of loop diuretics, concomitant use of thiazides, continuous intravenous infusion of diuretics, ultrafiltration, and peritoneal dialysis. Nevertheless, caution is advised since patients with HFpEF are sensitive to volume shifts due to high arterial and ventricular stiffness. They are more susceptible to intravascular volume depletion and may not tolerate “aggressive” decongestive therapies, such as intermittent high doses of loop diuretics and dialysis with high ultrafiltration rates. Alternatively, a combination of diuretics, continuous intravenous infusion, and low ultrafiltration rates may be better tolerated.¹

Heart transplantation (HT) is the gold standard therapy for treating advanced HF, but most patients with HFpEF may not be suitable for HT due to older age and comorbidities. Many patients with advanced HFpEF referred for HT have a specific etiology for HF, such as hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM) or infiltrative cardiomyopathies.¹² These patients have faced more difficulties to receive HT compared to those with HFrEF. Due to preserved LVEF and narrow LV cavity, patients with HFpEF are not usually treated with inotropes or left ventricular assist devices (LVAD). They usually stay longer on the waiting list for HT, as they are not categorized in priority status for HT, which is the condition in which most patients undergo HT in Brazil. Recently, changes in the prioritization rules have helped mitigate this problem in some regions, such as the 2020 update to Transplant System allocation criteria in the state of Sao Paulo, where intravenous diuretics dependence for patients with HCM or RCM was included as a #3 condition in the priority criteria, equivalent to inotrope dependence.¹⁴

Although LVAD have shown to improve morbidity and mortality in patients with HFrEF, their use remains limited

in patients with HFpEF. Due to small LV cavity and severe diastolic dysfunction, technical issues have occurred with LVAD in HFpEF.¹³ The use of Heartmate II, a continuous flow axial LVAD, was reported in 8 patients with advanced HCM and RCM, showing the occurrence of suck-down events of the LA.¹⁵ Simulation studies have been performed with LVAD in patients with HFpEF, and they appeared to result in beneficial hemodynamic effects, but these studies suggest avoiding a strategy with constant speed. Instead, they recommend using low pump speed at rest to prevent a suction event and high pump speed during exercise to prevent ineffective unloading.¹⁶ Because of these technical issues, which are related to anatomical and pathophysiological features of patients with HFpEF, the use of LVAD is still limited in this population.

Left atrial assist devices (LAAD) have also been proposed. LAAD can be implanted in mitral position pumping blood from the LA to the LV. Another LAAD (PulseVAD) pumps from the LA to the descending aorta.¹³ Although they are mechanistically interesting, clinical trials are needed to evaluate their roles in HFpEF.

The pathophysiology of advanced HFpEF also includes left atrium myopathy, and interatrial shunt devices (IASD) have been specifically developed to relieve symptoms by reducing LA pressure. A bare metal self-expanded device creating an 8-mm shunt, proven to be the optimal size to reduce LA pressure without overloading the right heart, was tested in a small randomized clinical trial, Reduced Elevated Left Atrial Pressure in Patients with HF (REDUCED-LAP-HF I).¹⁷ In 43 patients with LVEF $\geq 40\%$ and New York Heart Association functional class III/IV, the REDUCED-LAP-HF I trial showed a significant reduction in pulmonary capillary wedge pressure during exercise with IASD compared with the sham control group. This strategy is currently being tested in a larger multi-center randomized study, the REDUCED-

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LAP-HF II. Two other promising IASD, namely, the V-WAVE¹⁸ and the Atrial Flow Regulator,¹⁹ are also being evaluated in large randomized clinical trials.

Treatment of advanced HFpEF is evolving and the first step in its management is to recognize this condition. From the practical point of view, the proposed acronym “I NEED HELP” remains useful to identify potential patients with advanced HFpEF, but we suggest a few modifications and observations that are detailed in Table 2.¹²

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Table 2 – Warning signs of advanced HFpEF

| Acronym | Advanced HF alert | Comment for HFpEF |
|---------|---|--|
| I | Intravenous inotrope dependence | Unusual in HFpEF |
| N | Persistent NYHA III/IV; persistent elevation in natriuretic peptides | Natriuretic peptides are less elevated in HFpEF |
| E | End-organ dysfunction | Particularly renal dysfunction |
| E | Elevated filling pressures; severe diastolic dysfunction | Replacing the original LVEF below 20% |
| D | Defibrillator shocks (recurring appropriate shock) | Less common, unless there is a specific etiology (e.g. HCM) |
| H | Recurring HF hospitalizations and emergency department visits in the last 12 months | |
| E | Persistent edema, refractory to escalating diuretics | Diuretic management can be difficult |
| L | Low systolic blood pressure, persistently below 90 mmHg | Augmented BP sensitivity to volume shifts |
| P | Progressive intolerance to optimized medical therapy | Fewer drug options, but most can be considered if LVEF is below normal |

BP: blood pressure; HCM: hypertrophic cardiomyopathy; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

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