Echocardiography in Heart Failure with Preserved Ejection Fraction: From Primary Care to Tertiary Hospitals

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Introduction

Heart failure (HF) is a highly prevalent and incident clinical syndrome that mostly affects older adults. It is one of the main causes of hospital admission, which is a strong prognostic marker, considering that approximately 50% of hospitalized patients will be readmitted within 6 months.1

HF with preserved ejection fraction (HFpEF) is hemodynamically defined as an inability of the heart to meet adequate metabolic demands under normal filling pressures. This concept is fundamental, given that patients with normal left ventricular (LV) ejection fraction (EF) (> 50%) usually have normal cardiac output, but are only able to maintain this output at the expense of increased filling pressures. Some patients are known to show signs of congestion at rest, but the vast majority only presents clinical symptoms during effort.2

Echocardiography (ECHO) is the main tool used in this population. It is highly available, noninvasive, and easily applicable. However, EF assessment alone may not be sufficient to support the presence of HFpEF.

Concepts in the diagnosis of heart failure with preserved ejection fraction

HFpEF is currently defined as a clinical syndrome of HF with LVEF > 50% in the absence of a previously reduced EF. Patients’ symptoms fundamentally result from increases in LV filling pressures at rest or during effort. Documenting this increase in pressure using practical and reproducible means is one of the major challenges in the diagnostic process. Guidelines define HFpEF according to:3

1. Presence of signs and symptoms of HF
2. LVEF ≥ 50%
3. Absence of syndromes “simulating” HFpEF
4. Evidence of increased filling pressures or correlated noninvasive markers (elevated E/e’ ratio, increased left atrial volume, and increased levels of natriuretic peptides)

Clinical syndromes that mimic heart failure with preserved ejection fraction

Patients with HFpEF are typically older, obese, and female and have predisposing comorbidities such as hypertension, metabolic syndrome, lung disease, and renal failure. Differentiating a cardiac origin from noncardiac conditions is very difficult for the physician when faced with patients with nonspecific symptoms suggestive of HF, such as fatigue, reduced effort capacity, dyspnea on exercise, and lower limb edema. This is a very common problem in clinical practice.

Diagnostic scores

Two diagnostic algorithms – the HFPEF score and the HFA-PEFF algorithm of the European Society of Cardiology4,5 – assess pre-test probability in order to distinguish HFpEF from dyspnea of noncardiac origin. The combination of clinical and laboratory data, including electrocardiogram and ECHO analysis, will estimate whether the probability of HFpEF is low, intermediate, or high. The Emerging Topics Update of the Brazilian Heart Failure Guideline6 has objectively summarized this line of reasoning (Tables 1 and 2). Figure 1 shows how to apply these scores.

Echocardiography

We will now describe the main objective of our review, which consists of extracting the greatest number of data from this great diagnostic tool. Notice the amount of information obtained from ECHO when creating the HFA-PEFF score for HFpEF diagnosis (Table 2). In addition to ventricular diameters and LVEF calculation, an estimate of the pulmonary artery systolic pressure (PASP), the E/e’ ratio by tissue Doppler, the indexed left atrial volume (LAV), the indexed LV mass, the relative wall thickness (RWT) and, if possible, the study of myocardial deformation (global longitudinal strain) will be obtained. The accuracy of the variables provided by the ECHO will be analyzed, as well as how to use them.

Ejection fraction

LVEF should be obtained from a biplanar study, classically using Simpson’s method.7 The limitations of using EF assessment alone in decision making have been previously described.8 However, in the setting of HF, a LVEF > 50% is considered significant, thus starting the clinical reasoning within the HFpEF model.
Estimation of mean left atrial pressure in patients with normal ejection fraction

Careful quantification of cavity dimensions and volumes is extremely important before estimating filling pressures. The presence of structural changes, such as LV hypertrophy and/or left atrial (LA) dilatation, indicates a more marked cavity remodeling. The correct assessment of diastolic function will allow an adequate extraction of volume data. Diastolic dysfunction is a combination of abnormal ventricular relaxation, myocyte deformation, and LA function, culminating in elevated filling pressures.

The first step consists of analyzing the mitral flow pattern, known as the E/A ratio. In many cases, this pattern alone may be sufficient. Patients with an E/A ratio ≤ 0.8 and an E wave velocity ≤ 50 cm/s have a normal mean LA pressure, whereas those with an E/A ratio ≥ 2 have an elevated LA pressure. In intermediate cases, other variables will be used, such as the E/e’ ratio, indexed LAV, and peak tricuspid regurgitation velocity (TRV).

The relationship between flow velocity in early diastole (E wave, measured by pulsed Doppler) and mitral annular velocity (e’ wave, which represents mean septal and lateral annular velocities, measured by tissue Doppler) reflects the mean capillary pressure (CP). An E/e’ ratio ≥ 15 at rest has good diagnostic sensitivity in identifying an elevated CP, reinforcing the likelihood of HFpEF as the etiology of symptoms. However, an E/e’ ratio in the intermediate range (9-14) is much less sensitive and should not be used as an isolated echocardiographic parameter; the entire diagnostic algorithm should be used instead.

This algorithm showed good accuracy (84%) in identifying patients with HFpEF when applied to those with normal LVEF and complaints of fatigue during effort. Clinical evaluation, which included chest radiography and N-terminal B-type natriuretic peptide levels, was only 64% accurate. The use of these echocardiographic variables was also evaluated with regard to the prediction of hospital readmission in 30 days. When the E/e’ ratio was added to the clinical score, there was a 29% increase in the prediction of readmission risk.

Patterns of diastolic dysfunction are also prognostic markers, as they show changes in left atrial compliance, with atrial dilatation, mitral regurgitation, and atrial fibrillation (AF), the so-called progressive atrial remodeling (Figure 4). The indexed LAV represents a marker of chronic remodeling and is much more accurate than the diameter measure. In patients in sinus rhythm without valve disease, an indexed LAV > 34 mL/m² was an independent predictor of death, HF, and stroke. Different cut-off values are recommended for the indexed LAV in patients in sinus rhythm and patients with AF. Table 2 shows major and minor criteria according to the indexed LAV.

The PASP is calculated by peak TRV, using the modified Bernoulli equation (PASP = 4 x TRV squared, added to the estimated right atrial pressure). Elevated PASP, especially if associated with right ventricular (RV) dysfunction, is an important variable of poor prognostic in HFpEF. A peak TRV > 2.8 m/s indicates elevated PASP and represents an indirect marker of diastolic dysfunction.

Structural changes

Initial studies suggested that patients with HFpEF have concentric LV hypertrophy, which leads to reduced

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**Table 1 – H,FPEF score for the diagnosis of heart failure with preserved ejection fraction**

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Characteristics</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂</td>
<td>Heavy Hypertension: BMI &gt; 30 or 2 more anti-hypertensive drugs</td>
<td>2</td>
</tr>
<tr>
<td>F</td>
<td>Atrial fibrillation: Paroxysmal or persistent</td>
<td>3</td>
</tr>
<tr>
<td>P</td>
<td>Pulmonary hypertension: PASP &gt; 35 mm Hg (echocardiogram)</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Older patients: Age &gt; 60 years</td>
<td>1</td>
</tr>
<tr>
<td>F</td>
<td>Filling pressures: E/e’ &gt; 9</td>
<td>1</td>
</tr>
</tbody>
</table>

Source: Marcondes Braga et al. BMI: body mass index; PASP: pulmonary artery systolic pressure.

**Table 2 – H,PEFF score for the diagnosis of heart failure with preserved ejection fraction**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Major (2 points)</th>
<th>Minor (1 point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional</td>
<td>Septal e’ &lt; 7 and Lateral e’ &lt; 10 or E/e’ &gt; 15 or TRV &gt; 2.8 m/s (PASP &gt; 35 mm Hg)</td>
<td>E/e’ 9-14 or GLS &lt; 16%</td>
</tr>
<tr>
<td>Morphological</td>
<td>Indexed LAV &gt; 34 mL/m² or LV mass 149/122 g/m² (M/W) and RWT &gt; 0.42</td>
<td>Indexed LAV 29-34 mL/m² or LV mass &gt; 115/95 g/m² (M/W) or IVS or PW ≥ 12 mm</td>
</tr>
<tr>
<td>Biomarker (sinus rhythm)</td>
<td>NT-proBNP &gt; 220 pg/mL or BNP &gt; 80 pg/mL</td>
<td>NT-proBNP 125-220 pg/mL or BNP 35-80 pg/mL</td>
</tr>
<tr>
<td>Biomarker (atrial fibrillation)</td>
<td>NT-proBNP &gt; 680 pg/mL or BNP &gt; 240 pg/mL</td>
<td>NT-proBNP 365-660 pg/mL or BNP 105-240 pg/mL</td>
</tr>
</tbody>
</table>

GLS: global longitudinal strain; IVS: intraventricular septum; LAV: left atrial volume; M: men; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PASP: pulmonary artery systolic pressure; PW: posterior wall; RWT: relative wall thickness; TRV: tricuspid regurgitation velocity; W: women. Source: Marcondes Braga et al.
Figure 1 – Diagnostic flowchart of heart failure with preserved ejection fraction (HFpEF). ECG: electrocardiogram; ECHO: echocardiography; LVEF: left ventricular ejection fraction. Source: Marcondes Braga et al.6

Figure 2 – Diastole and volume estimation in heart failure. LA: left atrial; LV: left ventricular; PASP: pulmonary artery systolic pressure. Source: adapted from Nagueh SF.9

Echocardiographic parameters for estimating LV filling pressures

1 – Tricuspid regurgitation velocity
   Veloc máx IT 4,19 m/s
   PASP 70,3 mmHg

2 – Mitral annular velocity (tissue Doppler)
   V. e’ wave 6 cm/s
   V. a’ wave 3 cm/s

3 – Mitral flow velocity (pulsed Doppler)
   V. E wave 1.1 cm/s
   V. A wave 0.9 cm/s
   E/A ratio 1.22
   Ratio E/e’ 18

4 – Indexed LA volume

<table>
<thead>
<tr>
<th>Assessed parameter</th>
<th>Cut-off value</th>
</tr>
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<tbody>
<tr>
<td>Peak tricuspid regurgitation velocity</td>
<td>&gt; 2.8 m/s</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>&gt; 14</td>
</tr>
<tr>
<td>Indexed LA volume</td>
<td>&gt; 34 mL/m²</td>
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</table>
Algorithm for estimating LV filling pressures in patients with reduced or preserved EF/myocardial disease

<table>
<thead>
<tr>
<th>Mitral flow velocity (pulsatile Doppler)</th>
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<tbody>
<tr>
<td>E/A ratio ≤ 0.8 + E &gt; 50 cm/s</td>
</tr>
<tr>
<td>or</td>
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<tr>
<td>E/a &gt; 0.8 and &lt; 0.2</td>
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<table>
<thead>
<tr>
<th>3 parameters to be assessed</th>
<th>Cut-off value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak tricuspid regurgitation velocity</td>
<td>&gt; 2.8 m/s</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>&gt;14</td>
</tr>
<tr>
<td>Indexed LA volume</td>
<td>&gt;34 mL/m²</td>
</tr>
</tbody>
</table>

However, it is not always possible to obtain all 3 parameters

When only 2 parameters are obtained

- Normal LA pressure
- E/A ratio ≤ 0.8
- E ≤ 50 cm/s

All negative or 2 out of 3 negative

- 2 negative
- 1 positive/1 negative
- 2 positive

LA pressure cannot be estimated

Elevated LA pressure

All positive 2 out of 3 positive

- E/A ratio ≥ 2

Figure 3 – Diagnostic algorithm based on echocardiographic data. EF: ejection fraction; LA: left atrial; LV: left ventricular. Source: adapted from Nagueh SF.

LV diastolic function and filling pressures

- Normality pattern
  - E/A ratio > 1

- Relaxation deficit
  - E/A ratio < 1

- Restrictive pattern
  - E/A ratio > 2

- Pulsed Doppler
- Tissue Doppler

- Progressive worsening of diastolic dysfunction
- Progressive increase in mean LA pressure
- Progressive worsening of the functional class
- Progressive worsening of prognosis

Figure 4 – Patterns of diastolic dysfunction. LA: left atrial; LV: left ventricular. Source: personal archive.
distensibility and, consequently, elevated filling pressures.\textsuperscript{16} In addition, indexed LV mass has also shown a modest relationship with invasive measurement of filling pressures ($r = 0.41-0.48$).\textsuperscript{17,18} However, several studies have shown that many patients with HfPfEF exhibit concentric remodeling in the absence of hypertrophy or normal ventricular geometry.\textsuperscript{19-21} Corroborating this affirmation, LV hypertrophy was recently shown to be highly specific (88%) but not very sensitive (26%) in the diagnosis of HfPfEF, meaning that the absence of LV hypertrophy does not rule out HfPfEF.\textsuperscript{3} LV geometry is often classified using RWT, which consists of multiplying the LV posterior wall thickness (PWT) by 2 and dividing it by its end-diastolic diameter (EDD) ($RWT = 2 \times EPP/PWT$). There are four different patterns, described in Figure 5.

According to Table 2, assigned points differ according to mass and RWT values. Table 3 summarizes the accuracy of the main markers used.

When evaluating LV morphology, pathologies that mimic HfPfEF should be excluded. Whenever significant hypertrophy is identified, the diagnosis of amyloidosis should be considered, especially in the presence of pericardial effusion or apical sparing pattern (the LV apex is “spared” from involvement) by global longitudinal strain.\textsuperscript{22} In a series of patients with thicknesses > 12 mm, amyloidosis accounted for 13% of hospitalized patients with “HfPfEF”. Figure 6 shows an example of amyloidosis.

### Diastolic stress echocardiography – assessment of patients with dyspnea, normal left ventricular ejection fraction, and normal left atrial pressure at rest

Much of the difficulty in diagnosing HfPfEF is associated with the fact that filling pressures are often normal at rest and only become elevated during exercise testing. Thus, invasive cardiopulmonary exercise testing has emerged as the gold standard to confirm or exclude the diagnosis of HfPfEF as a cause of dyspnea.\textsuperscript{24,25} Recent studies have evaluated whether similar data can be obtained noninvasively using diastolic stress ECHO.\textsuperscript{26} Information acquisition during effort can unmask systolic and diastolic dysfunction. The most frequently studied parameters are the E/e’ ratio and peak TRV, which indicate increases in CP and PASP, respectively. The European Association of Cardiovascular Imaging and the American Society of Echocardiography recommend a staged protocol, preferably on a semi-supine bicycle, until the patient reaches the predicted

<table>
<thead>
<tr>
<th>Table 3 – Objective evidence of structural and functional cardiac abnormalities consistent with the presence of diastolic dysfunction/elevated left ventricular filling pressures</th>
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</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
<tr>
<td>Indexed LV mass</td>
</tr>
<tr>
<td>Relative wall thickness</td>
</tr>
<tr>
<td>Indexed LA volume</td>
</tr>
<tr>
<td>E/e’ ratio at rest</td>
</tr>
<tr>
<td>Peak tricuspid regurgitation velocity at rest</td>
</tr>
</tbody>
</table>

LA: left atrium; AF: atrial fibrillation; HfPfEF: heart failure with preserved ejection fraction; LV: left ventricle. Source: adapted from McDonagh.\textsuperscript{3}

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Figure 5 – Patterns of ventricular geometry. Source: adapted from Lang RM.\textsuperscript{7}

Figure 6 – Cardiac amyloidosis with extensive myocardial infiltration, valves, and interatrial septum. RV: right ventricle; RA: right atrium; LV: left ventricle; LA: left atrium. Source: personal archive.
maximum heart rate or develops limiting symptoms. The test is considered abnormal if the E/e’ ratio at peak stress is ≥ 15, with or without TRV > 3.4 m/s. It should be noted that increased TRV alone should not be used for the diagnosis of HFrEF, as it may simply represent a normal hyperdynamic response to effort, caused by increased pulmonary flow, even in the absence of diastolic dysfunction.27-29

In the presence of inconclusive results, one should consider performing an invasive stress test, measuring CP at rest and during effort (algorithm described in Figure 1).

Special cases
In patients with AF, the determination of the diastolic function pattern is compromised, given the absence of the A wave. However, filling pressures may be estimated using the E/e’ ratio or other variables. In cases of high filling pressures, the E-wave deceleration time and the isovolumetric relaxation time (IVRT) will be reduced.

In patients with pulmonary hypertension who develop RV overload, ventricular interdependence is usually altered, with a paradoxical septal movement. In these cases, only the lateral mitral annular velocity should be used, as the septal annular velocity will be reduced.

Another common situation, especially among older adults, is mitral annular calcification, which considerably reduces e’ wave velocity, overestimating the E/e’ ratio. In these cases, the E/A pattern on pulsed Doppler and the IVRT should be used instead of the E/e ratio.30,31

Conclusions
Diagnosing HFrEF is not simple, and the interaction between the clinician and the echocardiographer plays a key role in this process. The examiner has great responsibility and may even screen some patients in the outpatient setting, identifying higher risk phenotypes. Identifying specific imaging features can reduce the time until diagnosis; however, in most cases, clinical suspicion will be raised in a detailed report. There are controversies about the best indexes for obtaining LV filling pressures noninvasively, which are often tested in different settings and with different objectives. The adequate use of each discussed marker, respecting their limitations, will be of great value for the clinician in their etiological search.

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