

# Heart failure with preserved ejection fraction. What does it mean to a physician?

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## Introduction

Heart failure is a clinical syndrome caused by abnormal cardiac function resulting in characteristic symptoms such as oedema, breathlessness and fatigue. Cardiac functions are usually measured by echocardiography and an ejection fraction equal to or above 50% is considered as normal and less than 40% is considered as reduced. Most patients with heart failure have a reduced ejection fraction (HFrEF).

However, it is well known that patients with heart failure may have an ejection fraction of 50% or more; heart failure with preserved ejection fraction or HFpEF. Although this condition is largely underdiagnosed, it is a common form of heart failure as population-based studies have estimated the prevalence to be in the range of 30-75% depending on the criteria used in the diagnosis. According to a recent study, the prevalence of HFpEF in the hospitalized patient is about 20%.<sup>1</sup> Unlike in HFrEF, the diagnosis is not straight forward as patients usually are older and have multiple comorbid illnesses. Consequently, symptoms may be mistakenly attributed to these comorbid illnesses. The prevalence of HFpEF is rising due to increased aging population and consequently increased comorbidities, and is expected to overtake HFrEF in the next few years.<sup>2</sup> Because there is no proven treatment so far to improve outcome, the main emphasis is on prevention of HFpEF by controlling the risk factors and comorbidities.

## Pathophysiology

Diastolic dysfunction is considered to be the main abnormality of HFpEF. However, it is now believed that

there are several and more complex mechanisms involved in the pathophysiology of HFpEF. The pathophysiology could be due to a combination of haemodynamic and cellular mechanisms.

Among the haemodynamic mechanisms, left ventricular diastolic dysfunction causing increased stiffness and abnormal relaxation is the main pathophysiological abnormality.<sup>3</sup> This results in increased left ventricular filling pressure causing congestion of pulmonary veins leading to pulmonary hypertension.<sup>4</sup> The pulmonary hypertension ultimately leads to right ventricular dysfunction.

Volume expansion is another important mechanism<sup>5</sup> that is associated with right ventricular dilatation and increased volume of the heart causing pericardial restriction resulting in elevation of left ventricular filling pressure.<sup>6</sup>

Systemic microvascular inflammation is an important cellular mechanism caused by many comorbid conditions releasing mediators, which cause a profibrotic process leading to left ventricular remodeling and dysfunction.<sup>7</sup> The other types of cellular mechanisms include cardiometabolic abnormalities, cellular and extracellular structural changes in the cardiac myocytes and non-myocyte compartment causing diastolic dysfunction<sup>8</sup>.

## An approach to diagnosis

Clinical features of heart failure such as fatigue, weakness, dyspnoea and oedema can be nonspecific and can be caused by many non-cardiac conditions.

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Although history and examination alone are not sufficient to diagnose heart failure, presence of certain clinical features such as presence of jugular venous distention, prominent 3<sup>rd</sup> heart sound (gallop) and displaced apical impulse, significantly increase the likelihood of heart failure.<sup>9</sup> The Framingham criteria, which was developed five decades ago based on bedside clinical symptoms and signs, are still used in epidemiologic research to rule in heart failure (Table 1).<sup>10</sup> In patients suspected of heart failure, based on above mentioned high probability clinical features, a 2D echocardiogram is recommended for confirmation of heart failure. MICE (Male, Infarction, Crepitations, Edema) is another clinically useful and cost-effective decision-making rule developed using data from primary care setting has a very high accuracy for prediction of heart failure.<sup>11</sup> Accordingly, in patients presenting with suggestive symptoms, an echocardiogram is recommended only if they have either a history of myocardial infarction and basal lung crepitations, or in any male with ankle oedema. If these features are absent then an echocardiography is recommended only if the natriuretic peptides (NP) levels are raised above the cut off levels (BNP greater than 35 pg/ mL or NT pro-BNP level is greater than 125 pg/mL). The NICE guidelines recommend that in a patient presenting with symptoms of heart failure an echocardiography is recommended if they have a history of myocardial infarction.<sup>12</sup> Otherwise, a natriuretic peptide test should be performed and referred for echo only if they have levels above cut off values.

Although it is difficult to differentiate clinically from HFrEF, patients with HFpEF tend to have a distinct phenotype as they are more likely to be elderly, females and have cardio metabolic features: obesity, hypertension, diabetes and dyslipidaemia.<sup>13,14</sup> Furthermore, the prevalence of atrial fibrillation and anaemia are more common in HFpEF.<sup>15</sup>

### The definitive diagnosis

The definitive diagnosis of HFpEF ideally requires at least three conditions to be satisfied. Firstly, this condition should always be suspected in any patient who presents with clinical features suggestive of heart failure and a 2D echocardiogram showing normal ejection fraction (greater than or equal to 50%) with a non-dilated left ventricle (normal LVEDV) and no significant heart valve diseases.

Secondly, these patients should have an elevated level of natriuretic peptides (NP) above the cut off values (BNP >35 pg/mL and/or NT-proBNP >125 pg/mL). It is

important to remember that many cardiovascular and non-cardiovascular conditions like atrial fibrillation, older age and renal failure can cause of elevated NPs without having HFpEF.<sup>16</sup> Further, some obese patients may have HFpEF with NPs well below the cut off value.<sup>17</sup> Heart failure is unlikely if the plasma BNP level is less than 35 pg/mL or NT-proBNP less than 125 pg/mL. However, in patients with acute presentations, higher cut off values (BNP <100 pg/mL and NT-proBNP < 300 pg/mL) should be used to rule out acute heart failure.

Thirdly, it is important to demonstrate objective evidence of diastolic dysfunction using noninvasive tissue doppler 2D echocardiogram.<sup>18</sup> Transthoracic echocardiography is the ideal test to provide this hemodynamic information and detect typical structural changes like left ventricular hypertrophy or left atrial dilatation. However, these changes take time to happen and seen mostly in chronic HFpEF. The main change that mainly looked in to and found even in the early HFpEF is the strain on the LV wall. This is measured by the E and A waves of the mitral inflow and the E' of the septal and lateral walls. Depending on the values, it is divided in to 4 severities from Grade I to IV. One of the utmost important factors that has to be kept in mind is that Grade II is very much similar to a normal pattern, hence called 'Pseudo-normalization' if just the E and A waves measured. To rectify this, E' must be measured and the E/E' ratio must be calculated.

In patients presenting with unexplained dyspnea, a validated diagnostic H<sub>2</sub>FPEF score is a simple evidence-based approach to differentiate cardiac from non-cardiac cause by estimating the likelihood of HFpEF. This score ranges from 0-9 is made up of 6 bedside clinical and echocardiographic characteristics (Table 2).<sup>19</sup> A low probability score (0 to 1) is used to rule out and a high probability score (6-9) will establish the diagnosis of HFpEF with reasonable accuracy. An intermediate probability scores (2-5) identifies patients who will need additional assessment to establish the diagnosis.

Another category of heart failure with subnormal ejection fraction has been described recently and it is called HFmrEF (heart failure with mid-range ejection fraction) where the ejection fraction (EF) is between 40-49%.<sup>3</sup> These patients have a clinical profile and prognosis more like a HFpEF than HFrEF as they have only mild systolic dysfunction with features of diastolic dysfunction and usually categorized as HFpEF in clinical studies.<sup>20</sup> However, it is believed that HFmrEF may represent a temporary phase or an overlapping phase between HFpEF and HFrEF.<sup>21</sup>

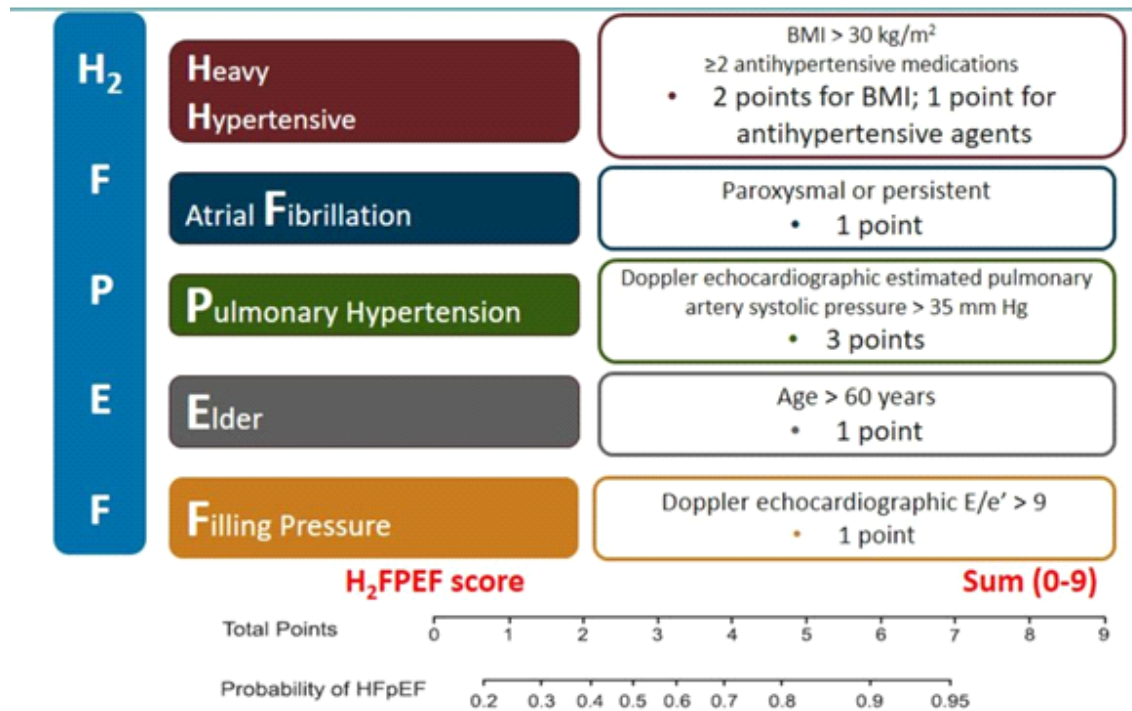
**Table 1.<sup>10</sup> Framingham criteria for diagnosis of heart failure**

Major criteria	Minor criteria
Acute pulmonary oedema	Ankle oedema
Cardiomegaly	Dyspnea on exertion
Hepatojugular reflux	Hepatomegaly
Neck vein distension	Nocturnal cough
Paroxysmal nocturnal dyspnoea	Pleural effusion
	Tachycardia (pulse>120bpm)

**Heart failures present with at least 2 major criteria or one major and 2 minor criteria**

**Table 2.<sup>19</sup>**

**H<sub>2</sub>FPEF Scoring**



## Treatment of HFpEF

Pharmacological treatment of HFpEF is currently not well established since unlike in HFrEF, there are no evidence-based treatments available for significant improvement of clinical outcomes in terms of mortality and morbidity. As such, current treatment of HFpEF aims at relieving symptoms and treating associated comorbidities.

Diuretics are beneficial for symptom relief caused by fluid overload.<sup>22</sup> When atrial fibrillation is associated with HFpEF, the resultant tachycardia and loss of atrial contraction can worsen diastolic dysfunction. Control of tachycardia with rate control medications such as beta blockers, calcium channel blockers and digoxin are beneficial for symptom relief.<sup>20,23</sup> Although treatment of hypertension is useful for prevention of HFpEF, there is no proven benefit in reduction of mortality and morbidity in patients with already established HFpEF.<sup>24</sup> Coronary artery disease is common in HFpEF and treatment with revascularization, where appropriate, has shown to improve mortality.<sup>25</sup>

There is evidence that low-dose spironolactone reduces hospitalization due to heart failure.<sup>26</sup> In older patients above 80 years with hypertension and HFpEF, there is significant reduction of heart failure when indapamide is given in addition to an angiotensin converting enzyme inhibitor.<sup>27,28</sup>

## Conclusion

HFpEF is an increasingly prevalent condition caused by interaction of heterogeneous conditions. Progress has been made on definition and diagnostic criteria. As physicians, a high index of awareness is necessary in order to make an early diagnosis as this can change the course of the disease by appropriate and aggressive treatment of the underlying risk factors and comorbid conditions. Delayed diagnosis has poor prognosis as no definite treatment is available at present. Patients with high probability symptoms of heart failure and those who satisfy the MICE or Framingham's criteria should undergo a 2D echocardiogram for confirmation. If the ejection fraction is  $\geq 50\%$  and the BNP is elevated above the cut of value, a proper tissue doppler echo study should be performed to make a definitive diagnosis of HFpEF. Alternatively, in those who present with unexplained dyspnea H<sub>2</sub>PEF scoring is a simple bedside and practical tool to diagnose or rule out HFpEF. The treatment is mainly to modify the risk factors and no disease modifying treatment is available at present. However, depending on the results of several ongoing trials, more promising treatment approaches are expected in the near future.

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