

When to Suspect Infiltrative or Storage Cardiomyopathy in Patients with HFpEF?

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Heart failure with preserved ejection fraction (HFpEF) is a frequent clinical syndrome, and it has accounted for 40% to 50% of heart failure hospitalizations in several reports published in the literature.^{1,2} It is a distinctly heterogeneous syndrome, and, with this diversity of scenarios, patients with a restrictive cardiomyopathy phenotype have been increasingly identified, especially elderly patients with cardiac amyloidosis.

Restrictive cardiomyopathies are diseases of the heart muscle that can arise due to various etiologies, including genetic abnormalities, infiltrative diseases, and storage diseases. From a pathophysiological point of view, they have in common the fact that they cause an increase in ventricular rigidity. Their real prevalence is unknown, but they are considered the least common form of cardiomyopathies.³ The infiltrative and storage diseases that can cause HFpEF include diseases with very different characteristics and evolution, such as amyloidosis, sarcoidosis, hemochromatosis, lysosomal disorders, and glycogen storage disorders.⁴

Reaching an etiologic diagnosis is a challenge, but the following clues should be followed during initial assessment:⁵ (1) Age – The restrictive forms in young adults (< 30 years of age) are largely due to genetic abnormalities that lead to increased fibrosis and abnormal deposition of iron, proteins, or glycogen. When it occurs in the elderly (> 65 years), cardiac amyloidosis predominates. (2) Family history – Autosomal dominant inheritance pattern suggests hereditary transthyretin amyloidosis or sarcomeric mutations, whereas X-linked inheritance indicates Fabry disease. (3) Clinical evaluation – Neuropathy may be found, and it suggests amyloidosis, whereas the presence of lymphadenopathy may accompany sarcoidosis. Fabry disease, on the other hand, may lead to cutaneous, neurological, and renal manifestations; (4) Electrocardiogram – low voltage, pseudoinfarction pattern, bundle branch blocks, and atrioventricular block suggest amyloidosis or sarcoidosis.

Keywords

Cardiomyopathies; Diagnosis; Heart Failure, Diastolic

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Over time, the assessment of cardiomyopathy with non-invasive methods has been improving and contributing to the diagnosis of these diseases.⁶ Figure 1 exhibits a proposal for a flowchart to be followed in patients with HFpEF and restrictive disease with the aim of facilitating the identification of patients with infiltrative and storage cardiomyopathy in this phenotype.

Transthoracic echocardiography represents the initial step in the diagnosis of HFpEF. In clinical scenarios where HFpEF presents with a restrictive pattern and increased left ventricular thickness, hypertensive heart disease and hypertrophic cardiomyopathy should be ruled out. In this scenario, infiltrative diseases grow in importance. Other findings in these patients include high filling pressures, normal left ventricular diameter, and highly dilated atria. Progressive atrial enlargement can lead to atrial arrhythmias and the development of secondary ventricular-atrial regurgitation. As a complement to echocardiography, cardiac magnetic resonance imaging stands out, with substantial added value for these diseases. Its image resolution more reliably defines the phenotype. Late enhancement obtained by means of gadolinium-based contrast can indicate alterations that are more suggestive of certain restrictive etiologies, differentiating them from constrictive pericarditis. Special sequences may even indicate the presence of myocardial edema and iron overload.^{5,7} More recently, T1 mapping has made it possible to quantify diffuse interstitial fibrosis, in a manner that differentiates etiologies of infiltrative and storage cardiomyopathy (amyloidosis and Fabry disease, for example).^{8,9}

The data obtained from imaging methods guide more specific tests, as follows: (1) pyrophosphate scintigraphy and/or biopsy studies for amyloidosis, (2) genetic tests for storage diseases, (3) positron emission tomography and biopsies for sarcoidosis, and (4) ferritin measurement and genetic testing for hemochromatosis.

Of all these diseases that can lead to myocardial restriction and, consequently, to HFpEF, cardiac amyloidosis is the one that stands out the most, and it warrants special attention. In 95% of cases, it is associated with deposition of transthyretin (ATTR) or light chains (AL). Currently, it is recognized that the ATTR form accounts for about 13% of HFpEF cases.¹⁰ A similar prevalence has been found in patients with severe aortic stenosis.¹¹ It is believed that the presence of amyloidosis, which is often undiagnosed, is one of the factors responsible for continued failures in trials on the treatment of HFpEF.¹² The diagnosis of cardiac amyloidosis, like the other diseases mentioned, requires a high degree of suspicion. Left ventricular wall thickness > 14 mm in conjunction

with fatigue, dyspnea, or edema, especially in the context of discordance between left ventricular thickness on the imaging method and QRS voltage on the electrocardiogram, in addition to compromised left ventricular longitudinal strain with apical preservation on echocardiography are findings that strongly suggest the presence of this disease.¹³ Magnetic resonance imaging has made it possible to increase diagnostic capacity by detecting the expansion of the myocardial

interstitium, leading to the classic pattern of diffuse delayed enhancement of gadolinium.⁵

An approach to definitive diagnosis capable of differentiating between the two main types of cardiac amyloidosis (AL and ATTR) has recently been published in the position statement proposed by the Department of Heart Failure (DEIC, acronym in Portuguese) of the Brazilian Society of Cardiology (Figure 2).¹⁴

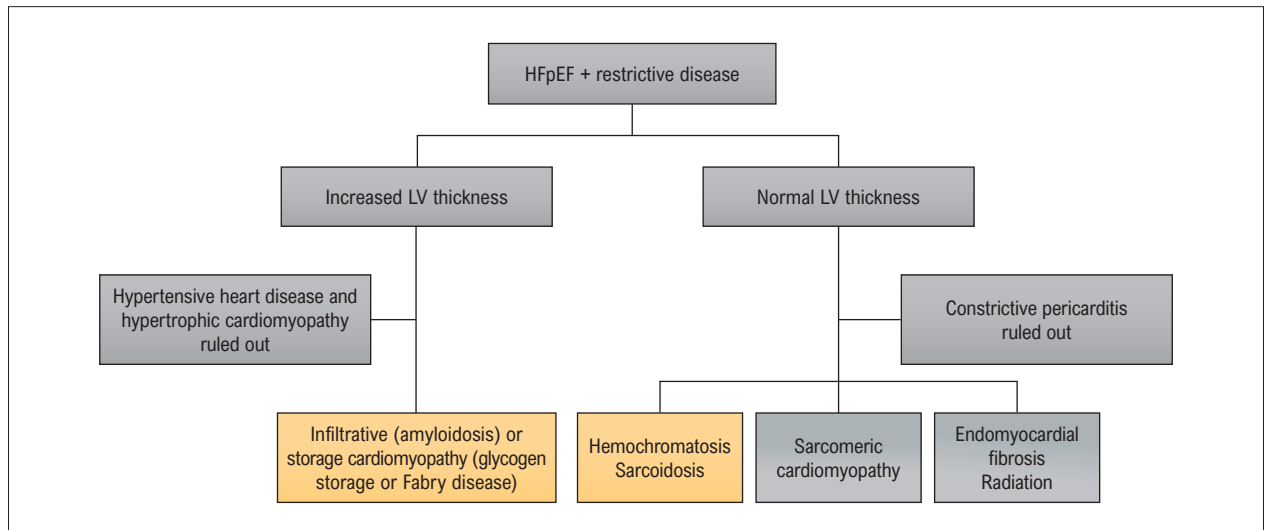


Figure 1 – Flowchart for investigation of heart failure with preserved ejection fraction and restrictive disease. HFpEF: heart failure with preserved ejection fraction; LV: left ventricle. Adapted from reference.⁶

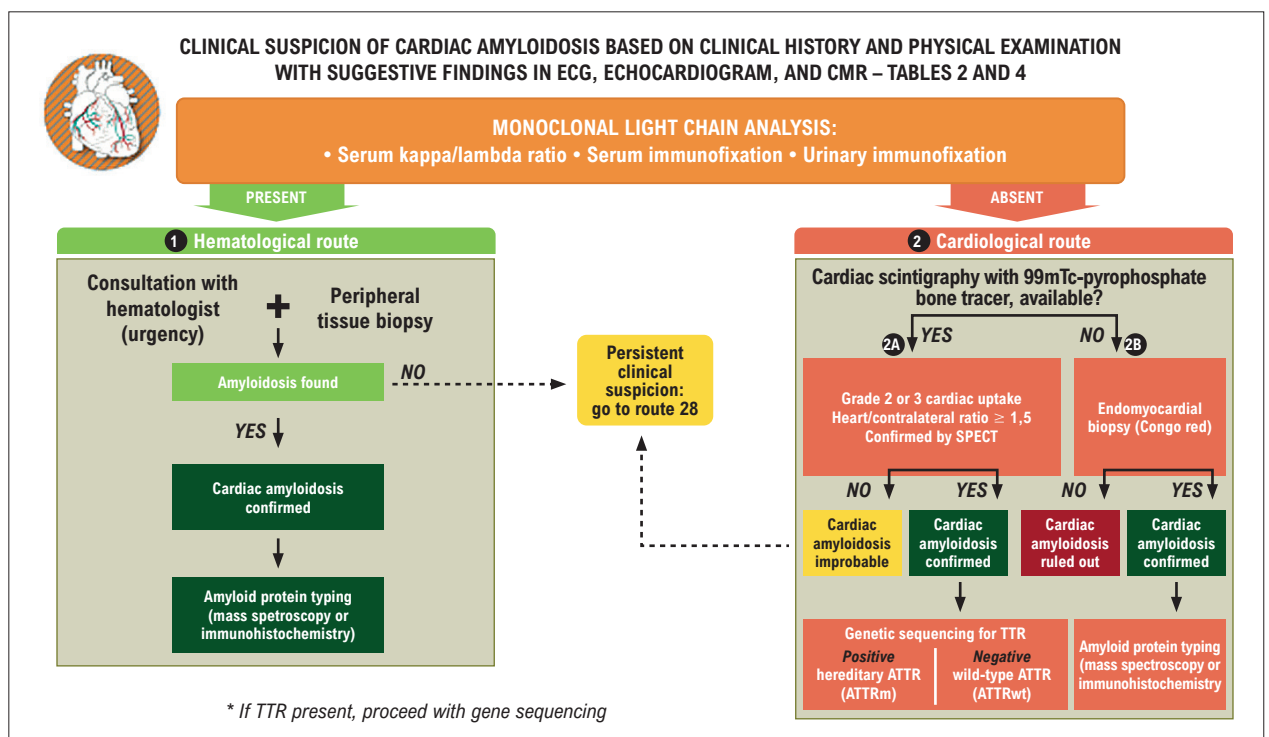


Figure 2 – Flowchart for investigation of cardiac amyloidosis.¹²

In conclusion, it is important to emphasize the investigation of specific phenotypes in patients with HFpEF, including infiltrative and storage diseases. Although some of these diseases are rare (Fabry, for example), others have established epidemiological relevance (such as amyloidosis), and it is fundamental to underscore that specific treatment alters the natural history of these patients.

Author Contributions

Writing of the manuscript: Bittencourt MI; Critical revision of the manuscript for important intellectual content: Bittencourt MI, Mourilhe-Rocha R.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.



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