

## Restrictive Cardiomyopathies: What's New on the War Front?

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### A rare – or not so rare – condition?

Restrictive cardiomyopathies, caused by primary pathologies of the heart muscle, are considered rare diseases, corresponding to about 5% of all cardiomyopathies.<sup>1</sup> The most frequent form of restrictive cardiomyopathy is cardiac amyloidosis (CA), which can be considered a benchmark since, with the availability of diagnostic technologies, its detection has been made much more frequent, associated with the fact that there are effective treatment possibilities.<sup>2</sup>

### Understanding based on pathophysiology

Restrictive pathophysiology of the left ventricle consists of increased myocardial stiffness, which leads to a sudden increase in chamber pressure at the beginning of ventricular filling in association with small filling volumes caused by wall hypertrophy or endomyocardial proliferation.<sup>3</sup> According to the European Society of Cardiology, restrictive cardiomyopathy can also be characterized by normal or reduced systolic and diastolic volumes (in one or both ventricles) and normal ventricular wall thickness. While this definition is conceptually accurate, its literal interpretation would lead to the exclusion of many common disorders with a restrictive physiology. Rapezzi et al.<sup>3</sup> recently classified restrictive cardiomyopathy as: 1) infiltrative, among which amyloidosis and sarcoidosis stand out; 2) storage diseases, mainly Fabry disease and hemochromatosis; 3) types related to interstitial fibrosis/intrinsic myocyte dysfunction; or 4) endomyocardial diseases (Figure 1).<sup>3</sup>

### Restrictive cardiomyopathy and heart failure with preserved ejection fraction

The clinical syndrome of restrictive cardiomyopathy mainly consists of diastolic dysfunction due to stiffness and thickening of the ventricular wall, filling restriction, and normal or near-normal systolic function.<sup>3,4</sup> This phenotype often presents as a syndrome of heart failure with preserved ejection fraction (HFpEF), and awareness of restrictive cardiomyopathy is essential in screening for HFpEF etiology. Recently, the Brazilian Guidelines for Heart Failure have suggested an algorithm for diagnosing HFpEF, which

points out the need to consider an etiological diagnosis, and restrictive cardiomyopathy is a potential focus of the so-called secondary etiology of HFpEF.<sup>5</sup>

### Cardiac amyloidosis: not so rare and already treatable

CA is an infiltrative disease caused by the deposition of fibrillar and insoluble protein aggregates in organs such as the heart, which leads to organ dysfunction. A 2022 systematic review<sup>1</sup> revealed that the prevalence of CA is 12% in HFpEF patients (95% CI 6%–20%), 8% in those diagnosed with aortic stenosis (95% CI 5%–13%), and 21% in autopsy findings in older adults (95% CI 7%–39%). Regarding diagnostic difficulty, a study in the United Kingdom with 1034 CA patients found a diagnostic delay of > 4 years, with an average of 17 hospitalizations in the 3 years preceding diagnosis. The same study evaluated the survival of patients after diagnosis, finding means of 31 months for variant transthyretin-related amyloidosis (ATTRv) and 57 months for wild type transthyretin amyloidosis (ATTRwt) ( $p < 0.0001$ ).<sup>2</sup>

Of the > 30 types of amyloidogenic proteins, there is greater evidence in the literature for 3. Immunoglobulin light chain-associated amyloidosis accounts for up to 12% of CA cases.<sup>1,4</sup> Changes in transthyretin protein, either through genetic mutation (ATTRv) or a wild protein that destabilizes and aggregates amyloid proteins (ATTRwt), account for up to 95% of CA cases.<sup>1</sup> TTR, a protein formed of 4 monomers that circulate as a tetramer, acts as a transporter of thyroxine and retinol (vitamin A). TTR forms amyloid fibrils when its tetramer is dissociated into monomers; the denaturation of the monomer allows incorrect assembly into aggregate structures. Different types of amyloidosis can cause different symptoms, so it is imperative that once amyloidosis is diagnosed, the precursor protein is studied to ensure correct treatment.<sup>1</sup>

In CA, the rate of adverse clinical outcomes rises rapidly after diagnosis because it is usually late. New imaging technologies and biomarkers are helping identify amyloidosis early,<sup>2,6</sup> although it formerly depended only on endomyocardial biopsy with the Congo-red technique, the gold standard for CA.<sup>4</sup>

Treatment consists of support for heart failure symptoms, of which the phenotypic manifestation of HFpEF is the most frequent. Congestion control is the main objective of therapy, for which loop diuretics are the most commonly used medication.<sup>3,4</sup> The clinical management of patients with CA is more difficult due to adaptation problems with established heart failure treatment. Angiotensin II converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, and calcium channel blockers are not well tolerated due to the increased risk of hypotension and bradycardia associated with autonomic dysfunction, which can negatively influence chronotropism. Additionally, non-dihydropyridine calcium channel blockers should be avoided in patients with cardiac or light chain-

### Keywords

Restrictive Cardiomyopathy; Diastolic Heart Failure; Amyloidosis; Sarcoidosis.

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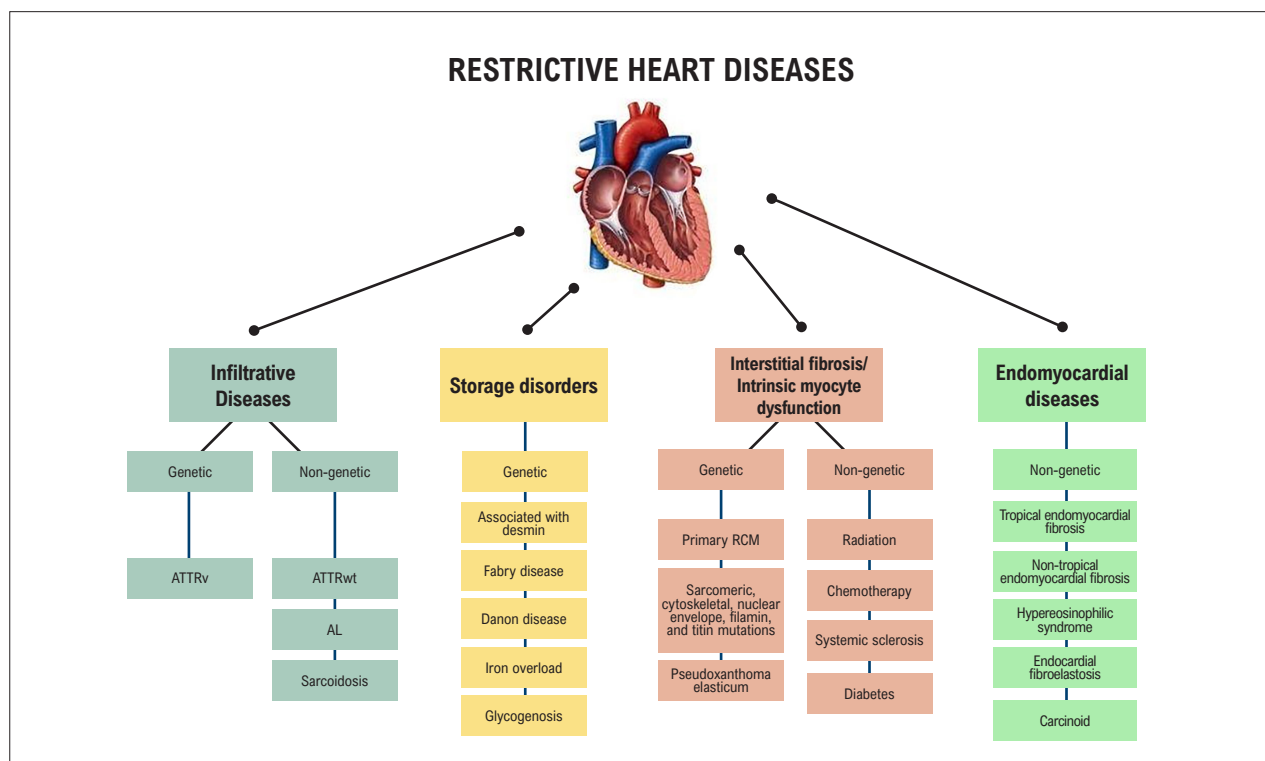
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**Figure 1** – Restrictive cardiomyopathies (RCM). ATTRv: variant transthyretin-related amyloidosis; ATTRwt: wild type transthyretin amyloidosis; AL: light chain-associated amyloidosis. Adapted from Rapezzi et al.<sup>3</sup>

associated amyloidosis, since they bind to amyloid fibrils, which can result in advanced heart blocks.<sup>4</sup> Furthermore, the structural, electrical and biochemical remodeling of the atrial chamber increases the incidence of atrial fibrillation, which is why anticoagulants should be prescribed to these patients in accordance with their CHA<sub>2</sub>DS<sub>2</sub>-VASc score (Figure 2).<sup>3,4,7</sup>

In addition to support for the clinical syndrome, there is a drug for the ATTRv and ATTRwt genotypes. Tafamidis (meglumine), a selective TTR stabilizer, binds to both thyroxine binding sites on the native TTR tetramer, preventing dissociation into monomers, which is the rate-limiting step in the process of amyloid fibril formation.<sup>4</sup> Tafamidis was tested in 441 patients in the ATTR-ACT trial,<sup>8</sup> which concluded that the drug is safe and can reduce mortality and hospitalization outcomes. In this trial, patients were randomized into 3 groups: 30 months of tafamidis 80 mg, 20 mg, or placebo. The 80 mg/day dose resulted in significantly higher survival than the 20 mg/day dose (RR = 0.70 [95% CI: 0.50 - 0.979; p = 0.0374).

#### Cardiac sarcoidosis: diagnostic updates

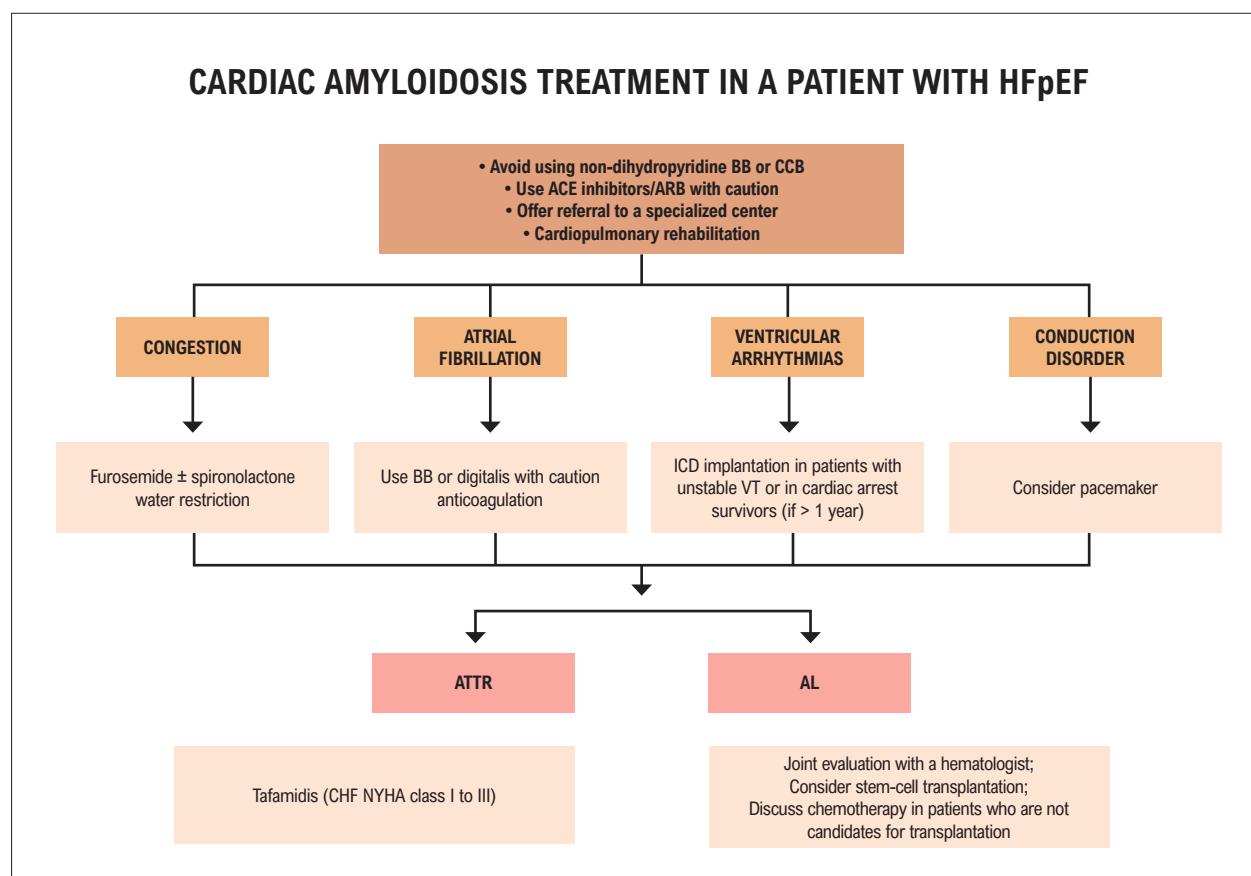
Sarcoidosis is a granulomatous inflammatory disease of unclear etiology that mainly affects young patients. The cardiac form of sarcoidosis represents 5% to 10% of diagnosed cases. However, as in CA, autopsy findings suggest that the prevalence is actually much higher. In 2019, the Japanese Circulation Society updated its diagnostic guidelines,<sup>9</sup> including clinical diagnosis of cardiac sarcoidosis when there

is evidence of non-caseating granulomas in organs other than the heart, in addition to some type of cardiac impairment, such as high-grade atrioventricular block, ventricular arrhythmia, atrial fibrillation, abnormalities in the ventricular wall, and/or contractile dysfunction of the left ventricle. The update also promotes, alongside <sup>67</sup>Ga scintigraphy and gadolinium-based magnetic resonance imaging, <sup>18</sup>F-fluorodeoxyglucose positron emission tomography when there is an abnormally high accumulation of markers in the heart as major diagnostic methods. This proposal was adapted in the current Brazilian Guideline for Myocarditis.<sup>10</sup>

#### Fabry disease

Fabry (or Anderson-Fabry) disease is a type of sphingolipidosis due to an X-linked inborn error caused by mutations in the GLA gene.<sup>11,12</sup> This mutation results in deficient enzymatic activity of  $\alpha$ -galactosidase A and, consequently, in lysosomal accumulation of glycosphingolipids, mainly globotriaosylceramide. Progressive accumulation of globotriaosylceramide leads to cellular dysfunction, causing inflammation, fibrosis and organ dysfunction, especially in the kidneys, brain, and heart.<sup>11</sup>

In November 2022, the Brazilian National Health Surveillance Agency (ANVISA) approved agalsidase  $\alpha$  (Replagal) as a specific treatment for Fabry disease. This drug, recommended for the classic form of the disease (for patients  $\geq 7$  years of age), is a recombinant form of the  $\alpha$ -galactosidase A enzyme and is produced in a human cell



**Figure 2** – Treatment of cardiac amyloidosis in patients with HFpEF. ACE: angiotensin-converting enzyme; AL: light chain-associated immunoglobulin amyloidosis; ARB: angiotensin receptor blockers; ATTR: transthyretin amyloidosis; BB: beta blockers; CCB: calcium channel blockers; CHF: chronic heart failure; HFpEF: heart failure with preserved ejection fraction; ICD: implantable cardioverter-defibrillator; NYHA: New York Heart Association; VT: ventricular tachycardia. Danzmann et al.<sup>7</sup>

line to provide a glycosylation profile that can influence uptake by mannose 6-phosphate receptors on the surface of target cells. This medication can only be prescribed to patients with a confirmed diagnosis of Fabry disease.<sup>12</sup> According to National Commission for the Incorporation of Technologies (CONITEC) protocol, patients with cardiovascular symptoms and systemic arterial hypertension are indicated for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, while those with dyslipidemia should receive statins. However, patients with arrhythmia and/or heart failure are to receive standard treatment.<sup>11</sup>

## Conclusions

Progress in classifying, diagnosing and treating restrictive cardiomyopathies offers us the opportunity to identify them earlier and reduce adverse outcomes in our patients. The contemporary approach to these cardiomyopathies must consider that the faster the definitive diagnosis can be established, the better the patient's prognosis will be.

## Author Contributions

Conception and design of the research and Acquisition of data: Danzmann LC, Feliciano LM, Kalil E, Siminovich

PL, Nora MM; Analysis and interpretation of the data and Critical revision of the manuscript for important intellectual content: Danzmann LC, Feliciano LM, Kalil E; Writing of the manuscript: Danzmann LC, Feliciano LM, Kalil E, Siminovich PL, Nora MM.

## Potential conflict of interest

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This study is not associated with any thesis or dissertation work.

## 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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