A Practical Approach to Differential Diagnosis of Cardiomyopathies with Infiltrative Phenotypes

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Introduction

Heart failure (HF) affects approximately 2% of the world population; heart failure with preserved ejection fraction (HFpEF) is responsible for approximately 50% of cases, and it has shown a progressive increase in prevalence with the aging of the population.¹

HFpEF is associated with high morbidity and mortality, and it is responsible for frequent hospitalizations, especially in the most elderly population. It has a complex pathophysiology and a diversified group of risk factors and etiologies. To date, few therapies have been shown to be effective in reducing cardiovascular outcomes in HFpEF; however, for specific etiologies, the possibility of disease-modifying therapeutic strategies exists.²⁻⁴

Restrictive cardiomyopathies (RCM) represent a small yet significant portion of patients with HFpEF, and they are characterized by diastolic dysfunction secondary to myocardial infiltration or primary dysfunction due to ventricular hypertrophy. RCM can result from hereditary or acquired diseases or a combination of both. Depending on their etiology, RCM are classified as infiltrative, non-infiltrative, storage diseases, and endomyocardial, and they may vary by age group. Some are more prevalent in certain regions (Table 1).⁵

The most common phenotypic characteristic of infiltrative RCM is increased ventricular wall thickness; amyloidosis and storage diseases are the main etiologies, and situations of hypertrophy (hypertensive cardiomyopathy, aortic stenosis, hypertrophic cardiomyopathy, and their phenocopies) are differential diagnoses (Figure 1). Due to the heterogeneous nature and variable phenotypic expression of RCM, diagnosis is a challenge; however, it plays a prognostic and therapeutic role. Early recognition remains a fundamental barrier to having an impact on survival in these cases.⁵⁻⁷ The objective of this publication is to assist clinicians in reasoning by means of a practical approach to differential diagnosis of RCM with infiltrative phenotypes.

Pathophysiology

Ventricular walls evolve with increased stiffness and reduced relaxation, resulting in impaired filling and consequent increase

in pressure while resting and, more intensely, during exertion; this severe diastolic dysfunction results in limited increases in end-diastolic volume of one or both ventricles. In addition, non-compliant ventricles inhibit rapid venous return, resulting in limited increases in stroke volume. Biatrial enlargement is characteristic; systolic function is generally preserved or slightly reduced, as is the size of the ventricular chambers, until advanced stages of the disease occur.^{5,7}

RCM do not have a uniformly accepted diagnostic criterion; additionally, the classic pattern of restriction can be found in other diseases that affect the heart. In a simultaneous hemodynamic study of the ventricles, initial diastolic pressure declines and rises rapidly, with a tendency to equalize end-diastolic pressures of both ventricles. This restrictive physiology has been attributed to a reduction in ventricular compliance secondary to fibrosis or an infiltrative process in the subendocardium and/or myocardium. In RCM, right atrial pressure usually exceeds 15 mmHg, and there should be a difference of at least 5 mmHg between right atrial pressure and pulmonary capillary pressure, as well as between the end-diastolic pressures of the left and right ventricles, due to the unequal involvement and compliance of both ventricles, unlike what is found in constrictive pericarditis, where equalization of ventricular filling pressures occurs.⁸

Clinical characteristics

HF is a common initial manifestation, and intolerance to physical exertion is a common complaint. Arrhythmias and conduction disturbances are often found due to progressive biatrial enlargement. Physical examination may reveal findings of pulmonary congestion and, especially, systemic congestion, including jugular stasis, hepatomegaly, ascites, lower limb edema, and the presence of B3 and B4; Kussmaul's sign is usually absent. Mitral and tricuspid regurgitation may be present.⁹ Thromboembolic complications, with or without concomitant atrial fibrillation, are not uncommon due to marked biatrial enlargement and low atrial contractility.¹⁰ The clinical phenotype of HF due to systemic diseases that affect the heart is very similar; however, extracardiac manifestations are varied, and they increase diagnostic suspicion of specific etiologies, in addition to family history of heart disease (Table 2).

Diagnostic investigation (Figure 2)

Laboratory exams

Troponin and NT-proBNP may be elevated, and they have prognostic value. Renal function can be altered when there is renal infiltration or in patients with advanced HF. When amyloidosis is suspected, free light chain assay and serum and urinary immunofixation have high sensitivity for diagnosing light chain amyloidosis (AL).

Keywords

Amyloidosis; Heart Failure; Cardiomyopathy, Restrictive

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Viewpoint

Table 1 – Classification of restrictive cardiomyopathies

Involvement of the myocardium	< 30 years	Age 30 to 65 years	> 65 years	Genetic
Non-infiltrative	Idiopathic	Idiopathic	Idiopathic	Acquired
	Scleroderma	Scleroderma		Acquired
		Elastic pseudoxanthoma		ABCC6
			Diabetic cardiomyopathy	Acquired
Infiltrative		ATTR Sarcoidosis		TTR gene variants*
			ATTR-WT**	Acquired
			AL amyloidosis	Acquired
	Sarcoidosis	Sarcoidosis		Acquired
Storage diseases	Hemochromatosis			HAMP, HFE, HFE2, HJV, PNPLA3, SLC40A1, TFR2
	Fabry disease			GLA
	Gaucher disease			GBA
	Hurler disease			IDUA
	Glycogen deposition***			Due to a specific type
		Iron overload	Iron overload	Acquired
Endomyocardial	Endomyocardial fibrosis			Acquired
	Eosinophilic syndrome	Eosinophilic syndrome	Eosinophilic syndrome	Acquired
		Carcinoid disease		Acquired
			Metastatic tumor	Acquired
			Radiation	Acquired
		Medication-related	Medication-related	Acquired

AL: light chain; ATTR: transthyretin amyloidosis; ATTR-WT: wild-type transthyretin amyloidosis

*V122I; I68L; L111M; T60A; S23N; P24S; W41L; V30M; V20I; APOA1

*** PRKAG2 gene disease, Danon disease (LAMP2)

Figure 1 – Differential diagnoses of heart failure with preserved ejection fraction. * Thickening of the left ventricular inferobasal wall and apical obliteration are frequent. ** Abnormal septal thickness (thickening or thinning). HF: heart failure; HFpEF: heart failure with preserved ejection fraction; LV: left ventricle; RCM: restrictive cardiomyopathy. Adapted from Pereira, N.L. et al. J AM Coll Cardiol. 2018; 71 (10)1130-48.

Table 2 – Specific characteristics and treatment of restrictive cardiomyopathies

Etiology	Clinical history	Extracardiac manifestations	ECG	Echo	NMR	Other methods	Treatment
Infiltrative restrictive cardiomyopathies							
Cardiac amyloidosis More than 30 proteins can lead to amyloidosis, 5 of which can lead to cardiac involvement; 95% are related to AL and TTR (mutation or WT)	Symptoms of HF Positive family history In TTR due to mutation, autosomal dominant inheritance	TTR: bilateral carpal tunnel syndrome, dysautonomia, Gastrointestinal tract alteration, peripheral neuropathy, sexual dysfunction WT: bilateral carpal tunnel syndrome AL: macroglossia, periorbital erythema	Normal to QRS complexes with low voltage, Anteroseptal/inferior pseudoinfarction	Hyperrefringence, biatrial enlargement, symmetric hypertrophy, preserved EF, apical sparing strain pattern	Diffuse or focal late enhancement may be subendocardial or transmural Increased ECV	AL: free light chain assay, serum and urinary immunofixation, if positive bone marrow and tissue biopsy (abdominal fat, endomyocardial) TTR: pyrophosphate scintigraphy in ATTR: presence of grade 2 or 3 or heart/contralateral ratio > 1.5 TTR: genetic testing Endomyocardial biopsy: Congo red and mass spectrometry	AL: chemotherapy, bone marrow transplant, consider heart transplant TTR: acting on RNA, blocking protein synthesis (patisiran and inotersen), stabilization of monomers (tafamidis, diflusal, and AG-10) and acting to remove already formed fibrils (doxycycline). Consider double transplantation (liver-heart) in TTR due to mutation and cardiac transplant in WT
Fabry disease X-linked recessive inheritance Alpha-galactosidase A deficiency, globotriaosylceramide accumulation	Symptoms of HF Positive family history	Neuropathic pain, heat intolerance, presence of angiokeratoma in the skin and/or mucous membranes, kidney injury, cornea verticillata, central nervous system injury	QRS with normal or extended amplitude, altered PR interval.	Symmetrical hypertrophy of the LV and RV wall, normal EF	Focal involvement, middle wall, inferolateral wall, normal or reduced ECV	Enzyme testing Genetic testing	Enzyme replacement therapy to control symptoms
Danon disease Dominant X-linked inheritance, caused by mutation of lysosomal-linked membrane protein 2 (LAMP2)	Symptoms of HF, ventricular arrhythmias	Skeletal myopathy, cognitive deficit	QRS with increased amplitude; short PR with delta wave	Major LV hypertrophy with possible outflow tract obstruction	Subendocardial late enhancement sparing the septum; normal or reduced ECV	Genetic testing	No specific treatment
Restrictive cardiomyopathies							
Sarcoidosis	Symptoms of HF, presyncope, syncope, arrhythmias, sudden death	Most frequently presents pulmonary involvement. It may present hepatic, spleen, ocular, lymphatic, cutaneous, nervous system, and renal involvement.	Arrhythmias, AVB, nonspecific repolarization changes	Thinning of the basal region of the interventricular septum, septal hypertrophy and aneurysms	Multi-focal myocardial involvement, sparing the edge of the endocardium; "mid-ventricular and subepicardial."	PET/CT with ¹⁸ F FDG for detection of the inflammatory process. Endomyocardial biopsy	Immunosuppression with a corticosteroid. In refractory cases, methotrexate, azathioprine, and mycophenolate mofetil Implantable defibrillator

Viewpoint

Continuation

Hemochromatosis	Weakness, arthralgia, skin hyperpigmentation, diabetes, liver cirrhosis, hypogonadism, hypothyroidism	Supraventricular arrhythmia	Presents restrictive diastolic dysfunction that progresses to dilation and systolic dysfunction	T2*	Ferritin assay, transthyretin saturation Genetic testing Therapeutic phlebotomy iron chelators
	Symptoms of HF Positive family history				
Endomyocardial fibrosis	Symptoms of HF, massive ascites disproportionate to lower limb edema, giant V wave	Arrhythmias (AF, AVB), low voltage QRS complexes	Normal EF. Thickening of the LV inferobasal wall, apical obliteration, and thrombi adherent to the endocardial surface. Pericardial effusion. Mitral and tricuspid regurgitation.	Late enhancement identified as a hyperintense linear image representing endocardial fibrosis or the double V sign	Angiography can be seen with left and right ventriculography show chamber distortion due to fibrosis and apical obliteration. Endomyocardial biopsy Consider myocardial resection surgery with ventricular reconstruction and valve replacement

AF: atrial fibrillation; AL: light chain; AVB: atrioventricular block; ECG: electrocardiogram; echo: echocardiogram; EF: ejection fraction; HF: heart failure; LV: left ventricle; NMR: nuclear magnetic resonance; RV: right ventricle; TTR: transthyretin

Electrocardiogram

Electrocardiogram (ECG) is very important to initiate diagnostic reasoning. Infiltrative disorders generate abnormal accumulations of substances in myocytes or in the interstitium of the myocardium, which are responsible for increased wall thickness; therefore, the voltage of the QRS complex may be reduced or incompatible with the degree of thickening in the presence of infiltration between myocardial fibers (a common finding in amyloidosis); on the other hand, when myocardial fibers are involved, we can observe an increase in QRS amplitude on ECG (Fabry disease, for example), with differential diagnoses of diseases related to increased afterload (arterial hypertension and aortic stenosis) and hypertrophic cardiomyopathy.¹¹ Although low voltage favors clinical reasoning of cardiac amyloidosis, it is present in only 20% of patients with the TTR form (transthyretin) and is more frequent in the AL form (50% of cases). The most common finding related to cardiac amyloidosis is the mismatch between increased ventricular thickness on echocardiogram and the amplitude of the QRS complex; another common finding is the presence of electrically inactive areas in the absence of obstructive coronary artery disease (pseudoinfarction).^{7,12} In Fabry disease, ECG abnormalities may include short PR interval, right bundle branch block, left ventricular hypertrophy, and giant negative T waves.¹³

In infiltrative RCM, sinus rhythm with biatrial overload may be observed. Atrial fibrillation, however, is not uncommon. Bundle branch blocks and atrioventricular blocks can also be a presentation of infiltrative diseases. Ventricular arrhythmias are also common.⁷

Echocardiography

Transthoracic echocardiography typically demonstrates normal ejection fraction, normal chamber volumes with biatrial enlargement, and restrictive diastolic filling parameters. Infiltrative RCM progresses with concentric increase in left ventricular wall and septum thickness; in amyloidosis, we may observe thickening of the right ventricle and interatrial septum. Assessment of left ventricular thickening on transthoracic echocardiography, especially when correlated with ECG, contributes to differential diagnoses in HFrEF (Figure 1). Diastolic compliance is abnormal, and it shows increased early diastolic filling velocity (E wave), reflecting elevated left atrial pressure, decreased atrial filling velocity (A wave) due to high ventricular diastolic pressures ($E/A > 1.5$), shortening of mitral deceleration time (< 120 ms), and decreased isovolumetric relaxation time. Tissue Doppler imaging reveals reduced initial diastolic longitudinal axis or mitral annular velocities (e') and increased E/e' ratio (> 15).

An aspect of myocardial hyperrefringence is often characteristic of amyloid infiltrate. Using the speckle tracking technique, the longitudinal strain pattern can help differentiate between cardiac amyloidosis and hypertrophic cardiomyopathy due to the characteristic of restricted basal movement compared to apical movement in amyloidosis (apical sparing).¹⁴⁻¹⁶

Figure 2 – Flowchart for investigation of restrictive cardiomyopathies with infiltrative phenotypes. * Reduced or normal QRS complex with mismatch between left ventricular wall thickness on echocardiography and QRS complex on electrocardiogram. ** Bone marrow and tissue biopsy of any affected organ (e.g. abdominal fat, endomyocardial). AL: light chain; AoS: aortic stenosis; BMB: bone marrow biopsy; ECG: electrocardiogram; ECV: extracellular volume; EMB: endomyocardial biopsy; HCM: hypertrophic cardiomyopathy; LGE: late gadolinium enhancement; MRI: magnetic resonance imaging; SAH: systemic arterial hypertension; TTRm: transthyretin mutation; TTR-WT: transthyretin, wild-type.

Viewpoint

Cardiac resonance

Cardiac magnetic resonance imaging, with a combination of native and contrast images, allows for accurate anatomical and functional assessment, as well as tissue characterization, indisputably assisting the assessment of RCM.¹⁷

Late gadolinium enhancement plays an established role in assisting differential diagnosis of cardiomyopathies, including restrictive ones. Diffuse subendocardial late enhancement is indicative of fibrosis, and it is observed in approximately one third of all cases of RCM; however, it is limited to patients with creatinine clearance above 30 mL/min. Gadolinium is an extracellular contrast agent, and, under normal conditions, it is not retained in the myocardium after administration. Amyloid infiltration results in volume expansion and contrast retention.

One of the greatest advantages of cardiac magnetic resonance imaging is tissue characterization of various structures and cardiac diseases. Recently, this characterization went from being merely qualitative to measuring objectively by means of T1 and T2 parametric maps, with the additional advantage of not requiring contrast. T1 mapping has made it possible to objectively measure areas of edema, inflammation, and fibrosis, reflecting systemic changes that occur in the extracellular space. Another advantage of the technique is that it allows measurement of extracellular volume (ECV), with contrast infusion, assisting in differential diagnosis of the restrictive infiltrative cause, given that, in amyloidosis, there is an increase in ECV. On the other hand, in diseases that occur with hypertrophy, there is a more reduced pattern of ECV.^{18,19}

Bone tracer scintigraphy

For suspected amyloidosis, this technique has demonstrated a sensitivity of 99% and specificity of 86% for diagnosis of cardiac involvement due to TTR cardiac amyloidosis, whether wild-type or due to a mutation, once the light chain form has been excluded. Radiopharmaceutical uptake is classified by the semi-quantitative visual score of cardiac retention in relation to the sternum; the presence of grade 2 or 3 is highly suggestive of TTR in the absence of monoclonal proteins. Furthermore, quantitative analysis of cardiac retention in ratio to the contralateral chest wall greater than 1.5 is consistent for diagnosis of the TTR form.²⁰

Endomyocardial biopsy

The evolution of imaging methods has reduced the need for endomyocardial biopsy in diagnosis, but it may still play a fundamental role in the diagnostic evaluation of patients with restrictive disease. Diagnoses of systemic diseases with cardiac involvement, such as amyloidosis and hemochromatosis, can be definitively established by biopsy of the right ventricle. Endomyocardial biopsy can be used when clinical, laboratory, and imaging data are not sufficient to establish diagnosis. It is worth underscoring

that a recent study observed that right ventricular biopsy was effective in only 29% of patients with unexplained RCM.²⁰

Genetic assessment

The genetic etiology of RCM is strongly suspected, due to its familial occurrence. Clinical and imaging presentations in infiltrative RCM are similar, and they may be difficult to differentiate when the extracardiac clinical expression is not as pronounced; correct genetic diagnosis implies prognostic assessment and specific therapeutic possibilities. In TTR amyloidosis, genetic analysis is essential to differentiate between mutation and wild-type; furthermore, mutational TTR is associated with the phenotypic expression of neuropathy and/or heart disease. It is also important in the differential diagnosis of hypertrophy, including hypertrophic RCM, its phenocopies, and storage diseases.²¹⁻²³

Treatment

Treatment of RCM must be individualized according to etiology (Table 2). Management of HF is a challenge, given that few pharmacological therapies have been associated with favorable outcomes in this scenario. Patients poorly tolerate antihypertensives and betablockers; digoxin should be avoided due to the risk of intoxication. Diuretic therapy and volume management is the most used strategy. Oral anticoagulation should be considered in the presence of atrial fibrillation, regardless of risk scores, due to the associated high thromboembolic risk. Pacemakers considered in blocks and symptomatic bradycardias and defibrillators are controversial.²³⁻²⁶

Conclusion

HFpEF is currently a great challenge for clinicians, as it represents a phenotype with many possibilities and, in general, limited therapeutic strategies; however, the search for etiologies should not be neglected, as it makes it possible to establish prognosis and specific therapeutic strategies that can modify the evolution of patients. For this purpose, all available workup should be taken into account, from clinical history and detailed physical examination, family history, and involvement of other systems, combined with adequate diagnostic procedures, including ECG, echocardiogram, laboratory tests, nuclear medicine, coronary and hemodynamic assessment, magnetic resonance, and, in specific situations, endomyocardial biopsy and genetic analysis. To paraphrase Claude Bernard, "If you do not know what you are looking for, you will not know how to interpret what you find." Therefore, we must not neglect considering and seeking differential diagnoses of HFpEF, including in RCM with infiltrative phenotypes.

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