

RESTRICTIVE CARDIOMYOPATHY

Definition

Restrictive cardiomyopathy (RCM) is a heterogeneous group of heart muscle diseases characterized by restrictive left ventricular and normal or decreased diastolic volume of either or both ventricles. Systolic function usually remains normal, at least early in the disease, and wall thickness may be normal or increased, depending on the underlying cause.¹⁻³ The disorders manifesting as RCM may be classified according to four main disease mechanisms: (i) interstitial fibrosis and intrinsic myocardial dysfunction, (ii) infiltration of extracellular spaces, (iii) accumulation of storage material within cardiomyocytes, or (iv) endomyocardial fibrosis.⁴ Restrictive cardiomyopathies are the least common of the cardiomyopathic disorders.

Pathophysiology

In typical RCM systolic function is less affected than diastolic function, and usually there is an abnormality of filling rather than of relaxation. Thus, in most cases there is rapid completion of filling of a poorly compliant ventricle in early diastole (E-wave), with little or no further filling in late diastole (A-wave). Though there is poor compliance of the ventricles, the peak filling rate is higher than normal, possibly as a result of augmented ventricular diastolic suction. The situation is thus analogous to pericardial disease causing constriction or tamponade.⁵ Usually patients with restrictive cardiomyopathy have normal ventricular volumes but raised filling pressures. In both constriction and restriction there is characteristically rapid completion of ventricular filling in early diastole so that the ventricular diastolic waveform has a dip and plateau (square root sign) configuration, but this is not always present.² Since the condition affects either or both ventricles, it may cause symptoms and signs of right or left ventricular failure. Infiltrative cardiomyopathies are characterized by the deposition of abnormal substances that cause the ventricular walls to become progressively rigid, thereby impeding ventricular filling. They may also produce hypertrophic or dilated cardiomyopathy patterns. Some of them increase ventricular wall thickness without actual myocyte hypertrophy, and occasionally even produce dynamic left ventricular outflow obstruction as may happen in amyloidosis, while others cause chamber enlargement with secondary wall thinning and global or regional wall motion abnormalities as may happen in sarcoidosis.⁶ Many disorders do not show restrictive pathophysiology throughout their natural history, but only at an initial stage (with an evolution towards a hypokinetic and dilated phenotype) or at a terminal stage (often progressing from a hypertrophic phenotype).⁴

Aetiology

Conditions associated with restrictive cardiomyopathy are presented in Figure 1. RCM in younger adults (<30 years of age) is largely due to genetic abnormalities that lead to increased fibrosis, abnormal deposition of iron, proteins, or glycogen. In older adults (>65 years of age) more common causes are cardiac amyloidosis, iron overload conditions, and radiation-induced heart disease.³

Syndromic and metabolic cardiomyopathies that may present with a restrictive pattern are discussed in the relevant Chapter.

Primary (Idiopathic) restrictive cardiomyopathy is expressed morphologically as myocyte hypertrophy and interstitial fibrosis.⁷ It can be familial with dominant inheritance and incomplete penetrance, and associated with skeletal myopathy and complete heart block. There is now clinical and genetic evidence demonstrating that restrictive cardiomyopathy is part of the spectrum of **sarcomeric** disease, and frequently coexists with hypertrophic cardiomyopathy in affected families.^{3, 8} To date, mutations have been mainly identified in the cardiac genes for the sarcomeric proteins troponin I (TNNI3) and beta-myosin heavy chain (MYH7) (Table 1).

Endomyocardial fibrosis and **Löffler endocarditis** (eosinophilic cardiomyopathy) are the main causes of obliterative cardiomyopathy. They are both associated with eosinophilia ($>1.5 \times 10^9/L$ for at least 6 months) that is either primary (Löffler), or secondary due to parasitic infections, lymphomas or vasculitis.^{1, 2} The intracytoplasmic granular content of activated eosinophils is responsible for the toxic damage to the heart with initial myocarditis and arteritis that are followed by a thrombotic stage, and eventually formation of extensive fibrosis that promotes further thrombotic material formation. Endomyocardial fibrosis is endemic in equatorial Africa, South America and Asia.⁹ The aetiology is not known. It seems likely that dietary, environmental, and infectious factors may combine in a susceptible individual to give rise to an inflammatory process leading to endomyocardial damage and scar formation.⁹

Anthracyclines can cause dilated cardiomyopathy or endomyocardial fibrosis. Diastolic dysfunction may persist even years after therapy with anthracyclines. The risk is greatly increased when there is a history of **irradiation** that causes myocardial and endocardial fibrosis, particularly in the right ventricle.¹

Carcinoid heart disease occurs as a late complication of the carcinoid syndrome (2.5 to 5.0 cases per 100,000 of the population per year) in 15% of patients, with tricuspid valve disease as the predominant lesion.^{10, 11} The development of cardiac lesions is correlated with circulating levels of serotonin and its principal metabolite, 5-hydroxyindoleacetic acid. The pathological lesion consists of fibrous plaques involving the tricuspid and pulmonary valves and the right ventricular endocardium.

Chloroquine and **hydroxychloroquine** in large cumulative doses (Kgs) may cause skeletal myopathy and restrictive cardiomyopathy.¹²

Presentation

The defining feature of RCM is the coexistence of persistent restrictive pathophysiology, diastolic dysfunction, non-dilated ventricles, and atrial dilatation, regardless of ventricular wall thickness and systolic function. Thus, the diagnosis of restrictive cardiomyopathy should be considered in a patient presenting with heart failure but no evidence of cardiomegaly or systolic dysfunction. Usually, patients present with fatigue and dyspnea. Angina does not occur except in amyloidosis, in which it may be the presenting symptom.² Patients may also present with thromboembolic complications. Cardiac conduction disturbances and AF are particularly common in idiopathic restrictive cardiomyopathy and amyloidosis. Approximately 10% of older patients undergoing carpal tunnel release surgery for idiopathic carpal tunnel syndrome have either TTR or AL amyloidosis in tenosynovial tissue, and this may be an early marker or precursor of amyloid heart disease.¹³ Heart block and ventricular arrhythmias are also common in cardiac sarcoidosis. Patients with iron overload cardiomyopathies may be asymptomatic or present with exertional shortness of breath. Severely overloaded patients develop advanced heart failure if left untreated and average survival is less than a year. Paroxysmal atrial fibrillation is the most common form of arrhythmia seen and is invariably associated with myocardial damage.

Signs and symptoms that raise suspicion of specific diagnoses are presented in the Chapter on Classification, Diagnosis and Principles of Therapy.

Physical examination

- **JVP** is elevated. A rapid x' descent and, especially, a prominent y' descent may be present in sinus rhythm.
- **Kussmaul's sign**, ie a rise or failure of JVP to decrease with inspiration, may be present, but typically occurs in constrictive pericarditis.
- **S₃** of LV or RV origin may be present.
- **Peripheral edema** or **ascites** and **enlarged and pulsatile liver** may be seen in progressed disease.

In advanced cases all typical signs of heart failure are present except cardiomegaly, although dilated ventricles may develop at later stages, particularly in patients with amyloidosis or sarcoidosis.

Investigations

Laboratory tests Hemoglobin, WBC, serum iron and ferritin, liver, renal, and thyroid function tests, and serum electrolytes should be taken at initial assessment. In suspicion of underlying disease specific tests, such as urine and plasma electrophoresis, serum free light chains for amyloidosis, and alpha-galactosidase levels are obtained.¹⁴ Peripheral eosinophilia is characteristic of Loeffler endocarditis.¹⁵ Elevated troponin, brain natriuretic peptide and uric acid are indices of adverse

prognosis in senile systemic amyloidosis.^{16, 17}

Chest X-ray reveals a normal cardiac size with possible atrial enlargement. Pulmonary congestion and pleural effusions may be present.

ECG shows non-specific ST-T changes with or without conduction abnormalities. The absence of increased voltage on ECG despite the appearance of echocardiographic hypertrophy can be the first clue to certain infiltrative diseases, such as cardiac amyloid or Friedreich ataxia. Low voltage and prolonged PR interval, and a pseudoinfarction pattern in the inferoseptal wall are typical signs of advanced amyloidosis. A decrease in QRS complex amplitude occurs because of myocyte atrophy along with decreased conduction velocity, and dyssynchronous activation resulting from amyloid deposition. However, infiltrative cardiomyopathies associated with increased size of cardiac myocytes may have increased voltage (e.g. Fabry disease).⁶ AV block suggests a desmin-related cardiomyopathy or amyloidosis.¹⁴

Two-dimensional echocardiography Ventricles are small with normal or increased wall thickness and the atria are usually dilated. Valvular regurgitation and atrial enlargement are more common in RCM than in constrictive pericarditis. Increased wall thickness in a non-dilated left ventricle is a prominent characteristic of cardiac amyloidosis (see Chapter 41).¹⁸ In advanced cardiac amyloidosis the typical ground glass (granular or sparkling) appearance of the myocardium as well as pericardial effusion may be seen.¹⁹ Two-dimensional echocardiography is diagnostic in the hypereosinophilic syndrome revealing the typical packing of both ventricular apices due to thrombus and usually significant MR. Akinetic segments are interspersed with normokinetic segments, resulting in an uneven wall motion abnormality may be seen in sarcoidosis.

Doppler echocardiography The pattern of mitral-inflow velocity reveals increased early diastolic filling velocity (E wave ≥ 1 m/sec), decreased late filling velocity (A wave ≤ 0.5 m/sec), increased E/A ratio (≥ 2), decreased deceleration time (≤ 150 msec), and decreased isovolumic relaxation time (≤ 70 msec). Pulmonary or hepatic vein patterns show that systolic forward flow is less than diastolic forward flow with increased reversal of diastolic flow after atrial contraction during inspiration.

In patients with amyloidosis, Doppler variables of diastolic dysfunction are typically present. New modalities such as *strain rate* and *speckle tracking* may be useful in diagnosing early amyloid infiltration.¹⁸

Cardiac catheterization The characteristic hemodynamic feature is a deep and rapid early decline in ventricular pressure at the onset of diastole, with a rapid rise to a plateau in early diastole. This is manifested as a prominent y descent followed by a rapid rise to a plateau, ie the dip and plateau or square-root sign. However, filling and the ventricular diastolic waveform are affected by heart rate, degree of hydration, and stage in the disease process, so that in some individuals filling is more gradual. The right atrial pressure is elevated, and the wave form is M- or W-shaped, as in constrictive pericarditis (see differential diagnosis). Usually, respiratory variation of venous pressure is absent, but the y descent may become deeper during

inspiration.

Electrophysiology study may be used for risk stratification of sudden cardiac death in patients with cardiac sarcoidosis and LVEF>35%.²⁰ It is also useful in patients with cardiac sarcoidosis and syncope.²¹

Cardiac magnetic resonance has a higher resolution than echocardiography and detects the presence of myocardial fibrosis.²²⁻²³ It is particularly useful in the diagnosis of infiltrative diseases such as sarcoidosis, amyloidosis, radiation-induced fibrosis, iron loaded cardiomyopathy, and constrictive pericarditis. In cardiac sarcoidosis CMR may be used for risk stratification of sudden cardiac death.²⁰ Myocardial extracellular volume (bolus or infusion technique) and pre-contrast T1, as well as T2 mapping, are biomarkers for cardiac AL and ATTR amyloid, and predict mortality in systemic amyloidosis.²⁴⁻²⁷ Phase-sensitive inversion recovery (PSIR) image reconstruction technique improves risk stratification in both primary and transthyretin-related amyloidosis.²⁸ Diffusion tensor cardiovascular magnetic resonance is a novel tool that offers discrimination between light chain and transthyretin cardiac amyloidosis.²⁹ CMR is necessary for diagnosis of iron load cardiomyopathy as well as for early differential diagnosis and staging of cardiac Fabry disease.³⁰

18 F-fluorodeoxyglucose (FDG) PET Imaging, and particularly combined PET-CT is also useful as a disease activity marker of both amyloidosis and sarcoidosis.^{31, 32}

Serum or urine electrophoresis and **bone marrow biopsy** are useful for the differentiation of various types of amyloidosis.²³

Bone scintigraphy has emerged as a cornerstone of transthyretin amyloidosis diagnosis, but scans may also be positive in AL amyloidosis.^{18, 33-35}

Technetium-labelled cardiac scintigraphy is a test in evolution for the diagnosis of transthyretin cardiac amyloidosis.³⁶

Gallium scintigraphy is a significant and independent predictor of ventricular arrhythmias in sarcoidosis.³⁷

Cardiac biopsy may be required in unexplained restrictive cardiomyopathy. A specific condition such as amyloidosis, iron storage disease, Fabry's disease, sarcoidosis, or glycogen storage disease may be diagnosed. However, non-specific histological features, such as interstitial fibrosis and myocyte hypertrophy are common, and patchy infiltration or less frequent location in the RV, as typically occurs in sarcoidosis, may obscure the diagnosis. Voltage-guided (through electroanatomical mapping) or advanced imaging-guided biopsy may be useful in this setting.^{20, 38} Amyloidosis cannot be excluded purely on the basis of light microscopy. Electron microscopy of myocardial tissue can confirm the diagnosis when light microscopy is negative, though care should be taken to distinguish between recently formed perimyocyte collagen and amyloid. The presence or absence of amyloid deposits in other organs is not absolutely predictive of cardiac involvement. When cardiac amyloid is suspected, **fat pad, salivary gland or rectal biopsies** are easier and safer alternatives.²³ **Abdominal fat pad needle aspiration** may also be useful, especially for ATTR-mutant

amyloidosis.³⁹

Liver biopsy is the gold standard for diagnosing hemochromatosis, but cardiac biopsy may be negative due to the patchy nature of an iron overload cardiomyopathy.

Differential Diagnosis

Restrictive hemodynamic characteristics may also be seen in cases of dilated or hypertrophic cardiomyopathy. However, the main problem is the distinction of RCM from constrictive pericarditis. The two conditions may also coexist, as happens in the cases of radiation fibrosis.² In the elderly, restrictive cardiomyopathy should be differentiated from age-related changes in diastolic compliance. Diagnosis of cardiac sarcoidosis and cardiac amyloidosis is presented in Chapter 41. Cardiac amyloidosis may mimic hypertrophic cardiomyopathy or hypertensive heart disease. Despite clinical, noninvasive, and hemodynamic assessment, the differentiation of restrictive cardiomyopathy from constrictive pericarditis remains difficult in a small subset of patients that present with mixed constrictive/restrictive physiology, as happens with radiation heart disease. Diagnosis of carcinoid disease is presented in Table 2.

Genetic testing

Genetic testing for DNA mutational analysis should be used to differentiate between senile and hereditary amyloidosis if TTR amyloid is detected from a biopsy specimen.^{34, 40} Mutated transthyretin genetic screening is warranted in elderly subjects with increased LVWT, particularly, those of African descent with neuropathy, carpal tunnel syndrome, ECG low voltage, or late gadolinium enhancement at MRI.⁴¹ Recommendations for genetic testing are presented in Table 3.

Therapy

General measures

Diuretics are used with caution to avoid inadvertent reduction of ventricular filling pressures.

There may be also extreme sensitivity to *beta blockers*. Beta-blockade is of no proven use and may aggravate hypotension, whereas calcium channel blockers generally worsen congestive heart failure.⁴²

ACEI/ARBs may also be used with caution.

Anticoagulation is recommended because of the propensity for thrombus formation in all types of RCM and particularly in endomyocardial fibrosis.

AF reduces cardiac output and rhythm control is recommended.

Permanent pacing and/or *ICD* may be required in conduction and arrhythmias (Table 6).

Transplantation may increase survival but in systemic disorders such as amyloidosis or sarcoidosis, recurrences may be seen in the transplanted heart.

Prognosis of **idiopathic restrictive cardiomyopathy** is better than in amyloidosis but relatively

poor in children.⁴³ Transplantation is the only therapeutic option in advanced cases.

Löffler's endocarditis may respond to steroids at early stages. Surgical decortication may be required in advanced cases of endomyocardial fibrosis but operative mortality is high (15-25%).² Most patients with this condition are dead within two years.²

Carcinoid heart disease with symptomatic RV failure may need surgery for tricuspid valve replacement and subsequent enlargement of the RV outflow tract (Table 2).^{11, 44}

Specific management of syndromic and metabolic causes of the restrictive phenotype are presented in the relevant Chapter.

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