Restrictive Cardiomyopathy

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Abstract

Restrictive cardiomyopathy (RCM) is a rare disease, characterized by increased stiffness of the ventricular walls, which causes heart failure because of impaired diastolic filling. In the early stages, systolic function may be normal, but when the disease progresses, systolic function usually declines as well. There is an overlap with other types of cardiomyopathy, such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and left ventricular noncompaction. Indeed, an autosomal dominantly segregating cardiomyopathy has been described where a single sarcomere gene mutation caused idiopathic RCM in some and HCM in other family members [1].

Introduction

Restrictive cardiomyopathy (RCM) is a rare disease, characterized by increased stiffness of the ventricular walls, which causes heart failure because of impaired diastolic filling. In the early stages, systolic function may be normal, but when the disease progresses, systolic function usually declines as well. There is an overlap with other types of cardiomyopathy, such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and left ventricular noncompaction. Indeed, an autosomal dominantly segregating cardiomyopathy has been described where a single sarcomere gene mutation caused idiopathic RCM in some and HCM in other family members [1].

According to the most recent AHA classification of cardiomyopathies [2], RCM is defined by restrictive ventricular physiology associated with normal or reduced diastolic volumes (of one or both ventricles), normal or near-normal systolic function, and normal or only mildly increased ventricular wall thickness. Several studies indicate that RCM is not a single entity; it is a heterogeneous group of disorders that can present with a spectrum of cardiac phenotypes [3].

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Classification of RCM is based on the underlying pathophysiological process: noninfiltrative, infiltrative, storage diseases, and endomyocardial (Table 8.1). Approximately 50 % of cases are caused by a specific clinical disorder, the majority in western countries being amyloidosis, whereas the remainder represents an "idiopathic" or "primary" process. RCM may also be associated with neuromuscular disorders, both congenital and acquired forms [4]. Hypertrophic cardiomyopathy may be particularly difficult to distinguish, since HCM in a late phase may start to dilate and wall thickness may appear normal or even reduced. Conversely, thickening of ventricular walls in cardiac infiltration or storage disease may resemble HCM. RCM must also be clinically distinguished from constrictive pericarditis, which is also characterized by abnormal ventricular filling with (near) normal systolic function.

Hereditary forms of RCM can be found in all subgroups, with both autosomal dominant and recessive genetic properties. Family history and investigation of first-degree relatives may therefore be important.

Molecular Background

Several inherited and acquired disorders may cause RCM, but many cases remain idiopathic. Familial RCM has been reported, but it remains uncertain whether this is a distinct genetic entity.

H.F. Baars et al. (eds.), *Clinical Cardiogenetics*, DOI 10.1007/978-3-319-44203-7_8

RCM may be due to myocardial fibrosis, hypertrophy, or infiltration of varying compounds, like amyloid or storage of, for example, glycogen. The terms hypertrophic and RCM do not refer to specific diseases, but are instead purely descriptive terms used to characterize myocardial disease associated with a broad spectrum of genetic syndromes or systemic diseases.

Cardiomyocyte contraction is dependent on intracellular calcium concentration and regulated by the troponin complex. *In vitro* studies have shown that RCM-causing mutations in TNNI3 show a greater increase in Ca^{2+} sensitivity than HCM-causing mutations, resulting in more severe diastolic impairment and potentially accounting for the RCM phenotype in humans [5].

The molecular background of different forms of RCM is highly variable, depending on the underlying cause, and will be discussed in more detail in specific clinical entities.

Clinical Aspects

Inability of the ventricles to fill limits cardiac output and raises filling pressures, leading to exercise intolerance and dyspnea. In most patients, venous pressure is elevated, which may lead to edema, ascites, and liver enlargement. Palpitations are often seen, with a relatively high occurrence of atrial fibrillation, which in turn may lead to rapid clinical deterioration due to high ventricular rates with short diastolic filling times. Third and fourth heart sounds may be present on physical examination.

Table 8.1 Classification of restrictive cardiomyopathy

			Genetic	Primary cardiac presentation	Common primary site or presentation
Myocardial	*Noninfiltrative*				
		Idiopathic restrictive cardiomyopathy	+	+	N.a.
		Scleroderma	±	–	Skin, joints, Raynaud, GI-tract, lungs
		Pseudoxanthoma elasticum	+		Skin, vascular wall (GI-tract)
		Diabetic cardiomyopathy		–	
	Infiltrative				
		Amyloidosis	±(AL)/+(AA)	+	AL: bone marrow, kidneys
					AA: peripheral neuropathy
		Sarcoidosis		±	Lungs
		Gaucher disease	+	–	Spleen, liver, bone marrow, bone
		Hurler disease	+	–	Bone, liver, spleen, brain
	Storage disease				
		Hemochromatosis	+		Liver, skin pigmentation, diabetes mellitus, arthropathy, impotence in male
		Fabry disease	+	+	Neuropathy, skin, kidney, stroke
		Glycogen storage disease	+	(+)/–	Hypoglycemia, muscle weakness, fatigability
Endomyocardial					
		Endomyocardial fibrosis	?	+	N.a.
		Hypereosinophilic syndrome	?	+	Systemic thromboemboli, neuropathy, GI-tract inflammation, lungs, bone marrow
		Carcinoid heart disease		–	Flushing, diarrhea, bronchospasm
		Metastatic cancers		–	N.a.
		Radiation		(+)[a]	N.a.
		Anthracycline toxicity		(+)[a]	N.a.
		Fibrous endocarditis caused by drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan)		+	N.a.

[a]Primary cardiac presentation after treatment of previous malignancy

Diagnosis

In typical cases, echocardiography, cardiac CT, or MRI will reveal normal or concentric thickened ventricles with normal or reduced intraventricular volumes. In contrast to hypertrophic cardiomyopathy, macroscopic hypertrophy and reduction of intraventricular volume are not pronounced. The atria are usually enlarged, sometimes exceeding ventricular volume. Systolic function may be normal or slightly reduced; diastolic function is reduced, with high E-wave, shortened deceleration time (<150 ms), and an E/A ratio of >2 on transmitral Doppler echocardiography (Fig. 8.1). Especially in infiltrative cardiomyopathies, the ECG may show low-voltage and nonspecific ST segment or T-wave abnormalities (Fig. 8.2). Cardiac catheterization shows a reduced cardiac output and elevation of left and right ventricular end-diastolic pres-

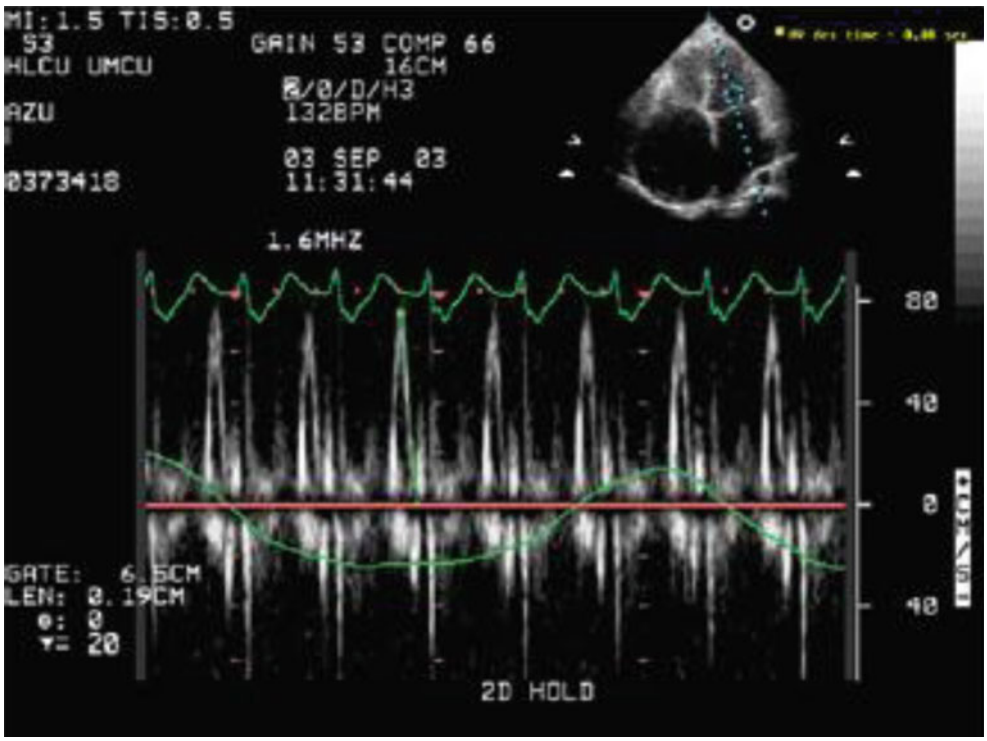

Fig. 8.1 2D-echocardiogram and transmitral Doppler signals in restrictive cardiomyopathy. In the upper part the 2D echocardiogram (apical four-chamber view) is shown, with normal sized ventricles (*top*) and huge atria below. In the main panel, the transmitral Doppler recording is shown in relation to the ECG, indicating E-waves with short deceleration time (*green line*) and almost absent A-waves (high E/A ratio)

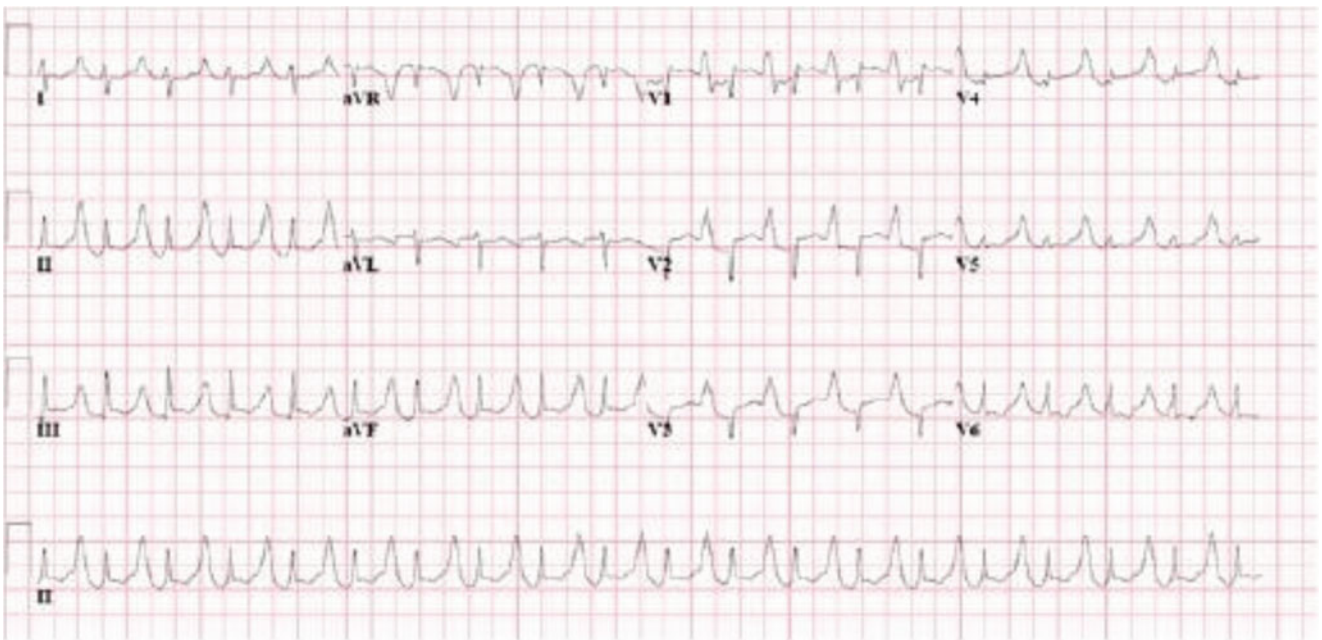

Fig. 8.2 ECG in restrictive cardiomyopathy. Low voltage abnormal QRS-complexes, preceded by huge P-waves in a 16-year-old girl with restrictive cardiomyopathy

sures with a dip-plateau representing an abrupt termination of filling in the first one third to one half of diastole. This configuration may resemble constrictive pericarditis; however, in constrictive pericarditis, there usually is a thickened pericardium, best seen on CT or MRI. In addition, interventricular dependence and respiratory variation of transmitral inflow on Doppler examination will be more pronounced in constrictive pericarditis; in difficult cases, volume challenge and simultaneous LV and RV pressure recording in relation to respiratory activity may be of help. Recently, tissue Doppler imaging was shown to reliably discriminate between the two conditions, with a cutoff value of >5 cm/s mean annular velocity (averaged from four walls) ruling out RCM [6]. Surprisingly, BNP values showed a large overlap between the two conditions.

The mainstay of diagnosis is endomyocardial biopsy, revealing fibrosis or the underlying specific infiltration or storage.

Clinical Approach and Differential Diagnosis

Since RCM often occurs in the setting of a systemic disease, in many cases the primary underlying disease is already known, like in Gaucher disease (GD), where noncardiac manifestations usually precede cardiac involvement. In these cases the clinical question may not be making the right diagnosis, but proving or excluding cardiac involvement. This may have consequences for the work-up; for instance, in case of a patient with known hemochromatosis, it may be best to start with cardiac MRI in order to find cardiac iron overload, whereas in suspected amyloidosis it may be best to start with endomyocardial biopsy.

Clinical history taking and clinical examination should be directed at symptoms indicative of underlying disease [4]. Ophthalmologic, otologic, dermatologic, gastroenterologic, nephrologic, hematologic, and neurologic examination may be necessary to help establishing a possibly treatable cause of RCM before the disease becomes intractable.

In apparently idiopathic RCM, it may be necessary to clinically exclude other causes of restriction, like hypertension, and to exclude the presence of specific infiltration or storage in an endomyocardial biopsy. In addition, taking an extensive family history including other phenotypes of cardiomyopathy and performing a genetic evaluation may be of help [7].

Treatment

In many cases, treatment is disappointing since myocardial damage is progressive and irreversible, with a possible exception for hemochromatosis and Fabry's disease (see below). In case of amyloidosis, aggressive anticancer treatment and/or bone marrow transplantation may slow progression of the disease, but this does not remove the already existing deposits of amyloid. In general, there is no specific medication for diastolic heart failure, other than diuretics to treat pulmonary or systemic congestion. The balance between pulmonary congestion due to fluid overload on the one hand, and forward failure due to too low filling pressures on the other hand, often is very delicate. Controlling heart rate with betablockers to allow adequate filling time is important; however, when restriction progresses, ventricular filling may no longer improve with longer diastole. In end-stage disease, a higher heart rate may even be the only way to compensate for a very low stroke volume. Atrial fibrillation occurs very often in RCM as a result of chronically elevated filling pressures and dilated atria, warranting oral anticoagulation to prevent stroke or embolism and adequate rate control when rhythm control is not possible anymore. Like in mitral stenosis and sinus rhythm, there is no consensus on the preventive use of anticoagulants in RCM and sinus rhythm. The only exception may be endomyocardial fibrosis (EMB) and hypereosinophilic syndrome, where endocavitary thrombosis and fibrosis with apical filling are thought to occur.

Heart transplantation may be an option in carefully selected cases, but due to the malignant nature or the multiorgan involvement of many underlying diseases, heart transplantation is often contraindicated. In idiopathic RCM, heart transplantation may offer good survival.

Prognosis

Prognosis is very much dependent on the underlying disease. In a study of 94 patients with idiopathic RCM after 68 months 50 % had died [8]. The causes of death were heart failure (47 %), sudden death (17 %), cancer (13 %), infection (13 %), and arrhythmias (11 %).

Idiopathic and Familial RCM

Idiopathic RCM is characterized by myocyte hypertrophy and interstitial fibrosis, with a restrictive hemodynamic pattern of the ventricles with reduced diastolic volumes, in the presence of normal or near-normal wall thickness and systolic function. By definition, there is no known underlying or related disease to explain cardiac involvement. In childhood, RCM is very rare, accounting for 2–5 % of pediatric cardiomyopathies [3]. About 30 % of children with RCM have a family history of cardiomyopathy and prognosis is poor (2-year mortality >50 %) [3]. In their study of 12 children, in one third, a mutation in genes coding for sarcomeric proteins was found; in the other two thirds, it was speculated that some might have been caused by mutations in genes encoding cytoskeletal or nuclear envelope proteins, more commonly

associated with DCM. Others might have been associated to – as yet unknown – inborn errors of metabolism or storage disorders with predominant cardiac involvement [3].

Familial RCM is an autosomal dominant cardiomyopathy with incomplete penetrance [9], generally considered in the absence of specific genetic abnormalities known to cause hypertrophic cardiomyopathy (HCM). However, some have suggested that RCM is part of the clinical expression of cardiac troponin I mutations [3]. A bundle branch block leading to complete heart block usually develops in the third or fourth decade [10]. Those who survive the fifth decade may develop a progressive myopathy [3, 11], although there are also reports of families with multiple affected individuals without skeletal myopathy [10]. Mogensen et al. [1] described a large family in which individuals were affected by either idiopathic RCM or HCM. Linkage analysis to selected sarcomeric contractile protein genes identified cardiac troponin I (TNNI3) as the likely disease gene. Several mutations were found, which also appeared to be present in six of nine unrelated RCM patients. They conclude that the restrictive phenotype is part of the spectrum of hereditary sarcomeric contractile protein disease. Changes in actin-binding affinity, affinity to troponin C, and the ability to inhibit thin filaments during diastole, caused by certain TNNI3 mutations, may lead to an altered interaction within the actin–troponin–tropomyosin complex, and thus may cause either severe diastolic dysfunction and RCM, or myocardial hypertrophy [12]. Myofilament hypersensitivity to cytoplasmic Ca^{2+} is a common feature that RCM-causing mutations share with HCM-causing mutations, with even more pronounced Ca^{2+} hypersensitivity in RCM [13].

Genetic engineering of adult cardiac myocytes [14] was used to identify effects of mutant cardiac troponin I (cTnI). The p.R193H mutant cTnI was associated with incomplete relaxation and acute remodeling to a contracted state as a direct correlate of the stiff heart characteristic of RCM in vivo. This occurred independently of Ca^{2+} concentration or sensitivity. Transgenic mice, expressing R193H cTnI in the heart, showed gradual changes in 12 months from impaired relaxation to diastolic dysfunction and eventually a phenotype similar to human RCM [15]. Treating RCM mice (caused by p.R193H mutant cTnI) with catechin was shown to cause myofibril desensitization and restoration of diastolic function [16]. These results demonstrate a critical role of the COOH-terminal domain of cTnI in the development of RCM. On the other hand, Cubero et al. [10] present a family of RCM patients with autosomal dominant inheritance, without signs of skeletal myopathy and no troponin I mutations.

Familial RCM may also occur as autosomal recessive or X-linked disease, and mutations in genes encoding *MYH7*, *TNNT2*, *ACTC1*, *MYPN*, and *TTN* have been described as rare causes of RCM [13, 17]. More recently, familial RCM could be related to a *FLNC* mutation; filamins are actin-cross-linking proteins, and filaminopathies can primarily affect the heart, apart from skeletal muscle disorders [17]. To make it even more complex, a recent study [15] described a unique family with autosomal dominant heart disease variably expressed as RCM, HCM, and dilated cardiomyopathy. They showed that a cardiac troponin T (*TNNT2*) mutation cosegregated with the disease phenotype. A missense mutation resulting in a p.I79N substitution was found in all nine affected family members, but none of the six unaffected relatives. Segregation analyses excluded a primary pathogenic role for eight other sarcomeric protein genes; however, this does not exclude a potential modifying effect of variants within these or other genes on cardiac phenotype [18].

RCM as Part of Specific Clinical Conditions with Known or Suspected Genetic Background (Selected Subjects)

Noninfiltrative Restrictive Cardiomyopathy

Scleroderma/Systemic Sclerosis

Apart from cardiac complications due to systemic or pulmonary hypertension, primary cardiac involvement can also occur in systemic sclerosis (SSc). Patchy myocardial fibrosis as a result of recurrent vasospasm of small vessels may lead to the clinical picture of RCM. Extensive fibrosis may be seen in patients with a long history of Raynaud phenomenon [19]. Familial clustering and ethnic influence have been demonstrated. Polymorphisms in genes coding for extracellular matrix proteins and cell-signaling molecules implicate non-MHC areas in SSc pathogenesis [20]. There are associations of polymorphisms in several genes with susceptibility and severity of SSc. All patients showed genetically predisposed high TGFbeta1 production, with polymorphisms at codons 10 and 25 of the TGFbeta1 gene [21]. Current data suggest that SSc is a multigenic complex disorder.

Pseudoxanthoma Elasticum

Pseudoxanthoma elasticum (PXE) is an inherited disorder that is associated with accumulation of mineralized and fragmented elastic fibers in the skin, vascular walls, and Bruch's membrane in the eye. It may lead to peripheral and coronary arterial occlusive disease as well as gastrointestinal bleedings. There is yet no definitive therapy. Recent studies suggest that PXE is inherited almost exclusively as an autosomal recessive trait. Its prevalence has been estimated to be 1:25,000–100,000. Very recently, the *ABCC6* gene on chromosome 16p13.1 was found to be associated with the disease. Mutations within *ABCC6* cause reduced or absent transmembraneous transport that leads to accumulation of extracellular material. Presumably, this mechanism causes calcification of elastic fibers.

In a study of 19 patients, it was found that systolic function was normal, but diastolic parameters were abnormal in seven patients [22]. Explanations for these abnormalities could be silent myocardial ischemia due to early coronary involvement and/or the direct consequences of ultrastructural defects of the elastic tissue of the heart.

Diabetic Cardiomyopathy

In diabetes mellitus, alterations in cardiac structure or function in the absence of ischemic heart disease, hypertension, or other cardiac pathologies is termed diabetic cardiomyopathy.

Structural changes include myocardial hypertrophy, fibrosis, and fat droplet deposition, initially leading to abnormal diastolic function. This phenotype is more prevalent in obese type 2 diabetic patients [23]. Advanced glycation endproducts (AGEs) are thought to be important in the pathophysiology of diabetic cardiomyopathy. Irreversible modification of proteins by glucose results in the formation of AGEs, a heterogeneous family of biologically and chemically reactive compounds with cross-linking properties. This process of protein modification is magnified by the high ambient glucose concentration present in diabetes [24].

The genetic background of diabetes is beyond the scope of this chapter. However, there are some very interesting studies pointing to a genetic link between diabetes and cardiac damage. Oxidative stress is known to be enhanced with diabetes, and oxygen toxicity may alter cardiac progenitor cell (CPC) function resulting in defects in CPC growth and myocyte formation, which may favor premature myocardial aging and heart failure. Ablation of the p66shc gene in a mouse model [25] prevented these negative effects, pointing at a possible genetic link between diabetes, reactive oxygen species, and the development of heart failure.

Infiltrative

Cardiac Amyloidosis

Amyloidosis comprises a group of diseases characterized by extracellular deposition of insoluble fibrillar proteins with concomitant destruction of normal tissue structure and function [26]. This results in stiffening and thickening of the myocardial walls, which can be easily demonstrated by echocardiography and often has a granular sparkling appearance. Absence of high ECG voltages further strengthens the suspicion of amyloidosis. Cardiac clinical manifestations include diastolic and systolic dysfunction, arrhythmias and conduction disturbances, orthostatic hypotension, coronary insufficiency, valvular dysfunction, and pericardial effusion.

Endomyocardial biopsy is the method of choice to diagnose cardiac amyloidosis and also allows characterization of the amyloid protein [27].

About 30 different proteins are known to form amyloid fibrils *in vivo*, of which only 11 have been identified that involve the heart [26]. The nomenclature is based on these proteins [28]. In clinical practice, however, amyloidosis is often classified as primary, secondary, hereditary, and age related.

Primary amyloidosis or *systemic AL amyloidosis* is the result of monoclonal immunoglobulin light chains secreted by clonal plasma cells (multiple myeloma) and predominantly deposited in the heart, kidney, and nerves. Congestive heart failure and conduction disturbances are frequent cardiovascular complications and often result in early death of the patients.

Although multiple myeloma is not considered a genetic disease, there are reports of around 130 families with two or more cases of multiple myeloma, MGUS or Waldenström's macroglobulinemia [29].

Secondary or systemic AA amyloidosis is associated with chronic diseases and manifested mainly in the kidney, liver and spleen, and, only rarely, in the heart. Proteinuria and renal failure are paramount.

Hereditary systemic amyloidosis is predominantly caused by deposition of amyloid fibrils derived from genetic variants of transthyretin (TTR), a transport protein synthesized mainly by the liver. More than 100 mutations are known already, of which the Val122I variant is the most common, occurring in 3 to 4 % of black Americans [30, 31]. Val122I reduces the stability of TTR tetramers, causing cardiac deposition of misfolded monomers and resulting in a cardiomyopathy typically during or after the sixth decade. Inheritance is often autosomal dominant with varying degree of penetrance [32, 33].Clinical syndromes include cardiomyopathy, nephropathy, and neuropathy. The presenting symptom often is the peripheral ascending neuropathy; cardiac involvement often is the final cause of death. On the other hand, the overall prognosis in Val122I carriers was not significantly different from noncarriers, as studied in a large community study by Quarta et al. [31]. The risk of heart failure was increased among carriers, suggesting that amyloidosis associated with the Val122I TTR variant may be more benign than previously thought.

Senile systemic amyloidosis is caused by the deposition of amyloid fibrils from normal nonmutant TTR, especially in the heart. It is age related, with male predominance and rare in patients younger than 60 years of age. Clinically it manifests as congestive heart failure, relatively frequently accompanied by carpal tunnel syndrome [30]. Progression of this disease is much slower than in AL amyloidosis, despite the more severe hypertrophy present in the senile form. Autopsy studies suggest that in up to 25 % of individuals over the age of 80 years, this type of TTR-derived amyloid can be found in the heart [33].

Sarcoidosis

Myocardial sarcoidosis generally occurs in association with other manifestations of the systemic disease, but primary cardiac symptomatology does occur. Cardiac infiltration by sarcoid granulomas may result in increased stiffness of the heart, with overt features of RCM. In addition, systolic dysfunction, conduction abnormalities, and arrhythmias may be seen. Treatment is empirically with glucocorticoids.

A genetic predisposition is likely, based on increased familial occurrence and different disease modes in different ethnic groups [34]. The strongest genetic associations are found within the human leukocyte antigen (HLA) antigens and functional polymorphisms within the butyrophilin-like 2 (BTNL2) gene [35].

Gaucher Disease

Although Gaucher disease (GD) is the most common lysosomal storage disease, it very rarely affects the heart (only subtype 3, occurring 1 in 200,000). It is caused by deficiency of glucocerebrosidase, which results in abnormal accumulation of glycolipids within cellular lysosomes. GD is one of the few inherited metabolic disorders that can be treated by enzyme replacement therapy with recombinant enzyme; early identification is crucial to improving ultimate outcome.

GD is inherited as an autosomal recessive disorder. The glucocerebrosidase gene is located on chromosome 1q21, and more than 180 distinct mutations are known. However, three mutant alleles account for most cases: p.N370S, p.L444P, and 84GG. The prevalence of these alleles varies with ethnicity. P.N370S is exclusively present in Ashkenazi Jews and non-Jewish Europeans, whereas p.L444P is common in northern Sweden. The diagnosis of GD is confirmed by the finding of reduced glucocerebrosidase activity in peripheral leukocytes. Diagnosis can also be confirmed by mutation analysis, which is an effective method for patient classification and carrier diagnosis.

Hurler disease

The mucopolysaccharidoses (MPS) are lysosomal storage disorders caused by the deficiency of enzymes required for the stepwise breakdown of glycosaminoglycans (GAGs), previously known as mucopolysaccharides. Fragments of partially degraded GAGs accumulate in the lysosomes, resulting in cellular dysfunction and clinical abnormalities. These are rare conditions, with an estimated total incidence of all types of MPS of approximately one in 20,000 live births. Hurler syndrome is the severe form of MPS I and is characterized by a broad spectrum of clinical problems including skeletal abnormalities, hepatosplenomegaly, and severe mental retardation. The incidence is approximately one in 100,000 births.

Cardiac abnormalities become apparent between birth and 5 years of age. These include cardiomyopathy, endocardial fibroelastosis, and valvular regurgitation, which on itself or combined may lead to heart failure. GAG storage within blood vessels causes irregular and diffuse narrowing of the coronary arteries and irregular lesions of the aorta. Coronary artery disease is often unrecognized until autopsy examination; it should be considered in affected patients with cardiac problems.

Mucopolysaccharidosis II (Hunter syndrome) is caused by a deficiency of iduronate 2-sulfatase (IDS), which results in storage of heparan and dermatan sulfate. MPS II is caused by mutations in the gene encoding for IDS, which is located on chromosome Xq28. Although the disorder is X-linked, cases in females have been reported on rare occasions.

Storage Diseases

Hemochromatosis

Iron-overload cardiomyopathy is often the result of multiple transfusions or a hemoglobinopathy, most frequently B-thalassemia. If cardiomyopathy occurs in the presence of diabetes, hepatic cirrhosis, and increased skin pigmentation, it may also result from familial hemochromatosis, an autosomal recessive disorder that arises from a mutation in the HFE gene, which codes for a transmembrane protein that is responsible for regulating iron uptake in the intestine and liver. The HFE gene is tightly linked to the HLA-A locus on chromosome 6p. The most common mutation is Cys282Tyr (C282Y), identified in 85–90 % of hemochromatosis patients in Northern Europe [36]. A second, relatively common HFE mutation (p.H63D) is not associated with clinically relevant iron overload but in case of compound heterozygosity with p.C282Y, iron overload can occur.

Cardiac involvement causes a mixture of systolic and diastolic dysfunction, often with arrhythmias. Cardiac dysfunction is due to direct toxicity from free iron and to adverse effects caused by myocardial cell infiltration, preferentially in the sarcoplasmic reticulum. The ventricles are more affected than the atria and the conduction system is often involved. Loss of myocytes occurs with replacement fibrosis. Macroscopically, the heart may be dilated or nondilated with thickened ventricular walls.

On cardiac MRI, a reduced T2* signal will be seen with increasing cardiac iron storage.

Phlebotomy and iron chelators like desferoxamine may reduce cardiac and other iron stores and result in clinical improvement.

Fabry Disease

This is an X-linked lysosomal storage disorder, caused by deficiency of lysosomal α-galactosidase A (GLA), leading to

the accumulation of glycosphingolipids in tissues like the heart. The ensuing ventricular hypertrophy is often classified as a RCM, although it may also resemble HCM. It is the second most prevalent lysosomal storage disease after Gaucher disease. The gene is located on the long arm (Xq22.1 region) of the X chromosome. Several hundred mutations in the gene have been identified.

The prevalence of Fabry disease is estimated to range from 1:17,000 to 1:117,000 males in Caucasians. Clinical manifestations are usually evident by the age of ten, often starting with neuropathy (burning pains of the palms and soles) and skin lesions (angiokeratomas). At higher age, cardiac and renal disease and stroke become more important. Cardiac involvement may lead to (symmetrical) ventricular hypertrophy, conduction defects, coronary artery disease, valve insufficiencies, and aortic root dilatation [37]. In general, cardiac involvement will be accompanied by other signs of Fabry disease, although these may be missed. Sometimes, the disease is limited to the myocardium. Therefore, screening for Fabry disease is advised in patients with otherwise unexplained LVH. Tissue Doppler may provide a preclinical diagnosis of cardiac involvement, even in patients without LVH. Echocardiographic appearance of Fabry disease may be distinguished from other forms of LVH based on a thickened, hyperechogenic layer in the endocardium and subendocardial myocardium, caused by local intracellular glycolipid deposition. This is paralleled by a hypoechogenic layer, representing the mildly affected midwall myocardium. A definitive diagnosis can be made based on a low plasma α-galactosidase A level in males or by endomyocardial biopsy, showing concentric lamellar bodies in the sarcoplasm of heart cells on electron microscopy. In females the diagnosis can be made by analysis of the GLA gene.

Although the disease is generally considered X-linked recessive, a better name would be X-linked semidominant. LVH may occur in heterozygous females in up to 64 %; end-stage renal disease and stroke may also develop and the overall negative effect on life span may be as much as 15 years.

Enzyme replacement therapy is available, albeit very expensive. Recombinant agalsidase-β may partly clear microvascular endothelial deposits in the heart and kidneys. Therapy can reduce LVH and enhance myocardial function.

Glycogen Storage Disease

Disorders of glycogen metabolism most often affect the liver and skeletal muscle, where glycogen is most abundant. To date, 12 subforms of glycogen storage disease (GSD) have been identified. The physiologic importance of a given enzyme determines the clinical manifestations of the disease. In general, hypoglycemia, hepatomegaly, and skeletal muscle weakness and easy fatigability are the predominant clinical features. In GSD type II (Pompe disease) and IIa (Danon disease), cardiac involvement may occur. The classic infantile form is characterized by cardiomyopathy and severe generalized muscular hypotonia [38]. The tongue may be enlarged. Hepatomegaly also may be present and is usually due to heart failure. Pompe disease is an autosomal recessive disorder with considerable allelic heterogeneity. It is caused by mutations in the gene encoding lysosomal alpha-1,4-glucosidase (GAA) located at 17q25.2-q25. More than 200 mutations have been reported [39].

Endomyocardial Causes of Restrictive Cardiomyopathy

Endomyocardial Fibrosis

Endomyocardial fibrosis (EMB) is an obliterative cardiomyopathy characterized by fibrotic thickening and obliteration of left, right, or both ventricles, with a predilection to selectively involve the apices and inflow region and spare the outflow tract. The fibrotic process does not affect the valve leaflets, the atria, or the great vessels, and extracardiac involvement is not known. There is a peculiar distribution of the disease in very specific areas within some countries around the equator [40]. In an epidemiological study of 214 families in Mozambique, 99 had no cases of EMB, 63 had one case, and 52 had more than one case [41]. The familial occurrence could be caused by genetic factors or susceptibility; however, this has not yet been elucidated. It may also rely on environmental factors, like the abundance of thorium and cerium in the soil, accompanied by magnesium deficiency. It has also been related to filariasis and altered immunological response to streptococcal infection in individuals whose immune status had been altered by parasitic infections

Hypereosinophilic Syndrome

Hypereosinophilic syndrome (HES) is a heterogeneous group of disorders characterized by unexplained persistent primary eosinophilia causing end-organ damage.

In the acute necrotic stage, there is endocardial damage, myocardial infiltration with eosinophils and lymphocytes, eosinophil degranulation, and myocardial necrosis. This phase may be clinically silent without abnormalities on echocardiography. However, serum troponin levels may be raised and contrast-enhanced MRI may detect myocardial inflammation. In the second stage, thrombus formation occurs along areas of damaged endocardium. This may lead to systemic embolization. In the third phase, progressive scar formation produces endomyocardial fibrosis and finally a RCM.

Apart from cardiac manifestations and thromboembolic (cerebral) complications, encephalopathy and peripheral neuropathy may occur.

One HES variant, myeloproliferative, is actually chronic eosinophilic leukemia, which has a unique genetic marker,

FIP1L1-PDGFRA, with consequences for the treatment [42]. Loeffler endocarditis, eosinophilic endomyocardial disease, or fibroplastic endocarditis appears to be a subcategory of the hypereosinophilic syndrome in which the heart is predominantly involved.

Autosomal dominant transmission of marked eosinophilia has been reported. In one family, the gene has been mapped to chromosome 5q31-33 [43].

MRI may be helpful in cases of RCM with luminal obliteration to differentiate perfused and enhancing myocardium from poorly vascularized and hypoenhancing thrombus or eosinophilic infiltrate [44].

Summary

RCM is a rare disease, often presenting with fatigue, exercise intolerance, or dyspnea. In many cases, RCM occurs as part of a multiorgan disease or malignancy, where cardiac involvement may occur early or late in time. Therefore, depending on clinical suspicion or other, noncardiac symptoms and findings, additional investigations are necessary before a definitive diagnosis can be made. The diagnosis of idiopathic RCM can only be made by exclusion. Idiopathic RCM sometimes presents as a familial or genetic form, related to mutations in the cardiac troponin I genes. There may also be overlap, both clinically and genetically, with family members with hypertrophic or dilated cardiomyopathy. Prognosis is often poor and treatment options are scarce: symptomatic therapy with diuretics and/or betablockers and occasionally specific therapy for the underlying disease.

References

1. Mogensen J, Kubo T, Duque M, Uribe W, Shaw A, Murphy R, Gimeno JR, Elliott P, McKenna WJ. Idiopathic restrictive cardiomyopathy is part of the clinical expression of cardiac troponin I mutations. J Clin Invest. 2003;111:209–16.
2. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;113:1807–16.
3. Kaski JP, Syrris P, Burch M, Tomé-Esteban MT, Fenton M, Christiansen M, Andersen PS, Sebire N, Ashworth M, Deanfield JE, McKenna WJ, Elliott PM. Idiopathic restrictive cardiomyopathy in children is caused by mutations in cardiac sarcomere protein genes. Heart. 2008;94:1478–84.
4. Stöllberger C, Finsterer J. Extracardiac medical and neuromuscular implications in restrictive cardiomyopathy. Clin Cardiol. 2007;30:375–80.
5. Gomes AV, Liang J, Potter JD. Mutations in human cardiac troponin I that are associated with restrictive cardiomyopathy affect basal ATPase activity and the calcium sensitivity of force development. J Biol Chem. 2005;280:30909–15.
6. Sengupta PP, Krishnamoorthy VK, Abhayaratna WP, Korinek J, Belohlavek M, Sundt 3rd TM, Chandrasekaran K, Seward JB, Tajik AJ, Khandheria BK. Comparison of usefulness of tissue Doppler imaging versus brain natriuretic peptide for differentiation of constrictive pericardial disease from restrictive cardiomyopathy. Am J Cardiol. 2008;102:357–62.
7. Hershberger RE, Lindenfeld J, Mestroni L, Seidman CE, Taylor MR, Towbin JA. Genetic evaluation of cardiomyopathy – a Heart Failure Society of America practice guideline. J Card Fail. 2009;15:83–97.
8. Ammash NM, Seward JB, Bailey KR, Edwards WD, Tajik AJ. Clinical profile and outcome of idiopatic restrictive cardiomyopathy. Circulation. 2000;101:2490–6.
9. Katritsis D, Wilmshurst PT, Wendon JA, Davies MJ, Webb-Peploe MM. Primary restrictive cardiomyopathy: clinical and pathologic characteristics. J Am Coll Cardiol. 1991;18:1230–5.
10. Cubero GI, Larraya GL, Reguero JR. Familial restrictive cardiomyopathy with atrioventricular block without skeletal myopathy. Exp Clin Cardiol. 2007;12:54–5.
11. Fitzpatrick AP, Shapiro LM, Rickards AF, Poole-Wilson PA. Familial restrictive cardiomyopathy wieth atrioventricular block and skeletal myopathy. Br Heart J. 1990;63:114–8.
12. Kostareva A, Gudkova A, Sjöberg G, Mörner S, Semernin E, Krutikov A, Shlyakhto E, Sejersen T. Deletion in TNNI3 gene is associated with restrictive cardiomyopathy. Int J Cardiol. 2009;131:410–2.
13. Nonaka M, Morimoto S. Experimental models of inherited cardiomyopathy and its therapeutics. World J Cardiol. 2014;6:1245–51.
14. Davis J, Wen H, Edwards T, Metzger JM. Thin filament disinhibition by restrictive cardiomyopathy mutant R193H troponin I induces Ca2+-independent mechanical tone and acute myocyte remodeling. Circ Res. 2007;100(10):1494–502.
15. Du J, Liu J, Feng HZ, Hossain MM, Gobara N, Zhang C, Li Y, Jean-Charles PY, Jin JP, Huang XP. Impaired relaxation is the main manifestation in transgenic mice expressing a restrictive cardiomyopathy mutation, R193H, in cardiac TnI. Am J Physiol Heart Circ Physiol. 2008;294:H2604–13.
16. Zhang L, Nan C, Chen Y, Tian J, Jean-Charles PY, Getfield C, Wang X, Huang X. Calcium desensitizer catechin reverses diastolic dysfunction in mice with restrictive cardiomyopathy. Arch Biochem Biophys. 2015;573:69–76.
17. Brodehl A, Ferrier RA, Hamilton SJ, Greenway SC, Brundler MA, Yu W, Gibson WT, McKinnon ML, McGillivray B, Alvarez N, Giuffre M, Schwartzentruber J, Gerull B, FORGE Canada Consortium. Mutations in FLNC are associated with familial restrictive cardiomyopathy. Hum Mutat. 2016;37:269–79.
18. Menon SC, Michels VV, Pellikka PA, Ballew JD, Karst ML, Herron KJ, Nelson SM, Rodeheffer RJ, Olson TM. Cardiac troponin T mutation in familial cardiomyopathy with variable remodeling and restrictive physiology. Clin Genet. 2008;74:445–54.
19. Tzelepis GE, Kelekis NL, Plastiras SC, Mitseas P, Economopoulos N, Kampolis C, Gialafos EJ, Moyssakis I, Moutsopoulos HM. Pattern and distribution of myocardial fibrosis in systemic sclerosis: a delayed enhanced magnetic resonance imaging study. Arthritis Rheum. 2007;56:3827–36.
20. Johnson RW, Tew MB, Arnett FC. The genetics of systemic sclerosis. Curr Rheumatol Rep. 2002;4:99–107.
21. Crilly A, Hamilton J, Clark CJ, Jardine A, Madhok R. Analysis of transforming growth factor beta1 gene polymorphisms in patients with systemic sclerosis. Ann Rheum Dis. 2002;61:678–81.
22. Nguyen LD, Terbah M, Daudon P, Martin L. Left ventricular systolic and diastolic function by echocardiogram in pseudoxanthoma elasticum. Am J Cardiol. 2006;97:1535–7.

23. Seferović PM, Paulus WJ. Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes. Eur Heart J. 2015;36:1718–27.
24. Brownlee M (1994 Jun) Lilly Lecture 1993. Glycation and diabetic complications. Diabetes 43(6):836–841
25. Rota M, LeCapitaine N, Hosoda T, Boni A, De Angelis A, Padin-Iruegas ME, Esposito G, Vitale S, Urbanek K, Casarsa C, Giorgio M, Lüscher TF, Pelicci PG, Anversa P, Leri A, Kajstura J. Diabetes promotes cardiac stem cell aging and heart failure, which are prevented by deletion of the p66shc gene. Circ Res. 2006;99:42–52.
26. Maleszewski JJ. Cardiac amyloidosis: pathology, nomenclature, and typing. Cardiovasc Pathol. 2015;24:343–50.
27. Kholova I, Niessen HWM. Amyloid in the cardiovascular system: a review. J Clin Pathol. 2005;58:125–33.
28. Selvanayagam JB, Hawkins PN, Paul B, Myerson G, Neubauer S. Evaluation and management of cardiac amyloidosis. J Am Coll Cardiol. 2007;50:2101–10.
29. Ogmundsdóttir HM, Einarsdóttir HK, Steingrímsdóttir H, Haraldsdóttir V. Familial predisposition to monoclonal gammopathy of unknown significance, Waldenström's macroglobulinemia, and multiple myeloma. Clin Lymphoma Myeloma. 2009;9:27–9.
30. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, et al. Systemic cardiac amyloidosis. Disease profiles and clinical courses of the 3 main types. Circulation. 2009;120:1203–12.
31. Quarta CC, Buxbaum JN, Shah AM, Falk RH, Claggett B, Kitzman DW, Mosley TH, Butler KR, Boerwinkle E, Solomon SD. The amyloidogenic V122I transthyretin variant in elderly black Americans. N Engl J Med. 2015;372:21–9.
32. Hesse A, Altland K, Linke RP, Almeida MR, Saraiva MJ, Steinmetz A, Maisch B. Cardiac amyloidosis: a review and report of a new transthyretin (prealbumin) variant. Br Heart J. 1993;70:111–5.
33. Ruberg FL, Judge DP, Maurer MS. Familial amyloid cardiomyopathy due to TTR mutations: an underground cause of restrictive cardiomyopathy. Letter to the editor.J Card Fail. 2009;15:464.
34. Grunewald J. Genetics of sarcoidosis. Curr Opin Pulm Med. 2008;14:434–9.
35. Spagnolo P, Sato H, Grutters JC, Renzoni EA, Marshall SE, Ruven HJ, Wells AU, Tzouvelekis A, van Moorsel CH, van den Bosch JM, du Bois RM, Welsh KI. Analysis of BTNL2 genetic polymorphisms in British and Dutch patients with sarcoidosis. Tissue Antigens. 2007;70:219–27.
36. Pietrangelo A. Hereditary hemochromatosis – a new look at an old disease. N Engl J Med. 2004;350:2383–97.
37. Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C, Linhart A, Sunder-Plassmann G, Ries M, Beck M. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Investig. 2004;34:236–42.
38. Howell RR, Byrne B, Darras BT, Kishnani P, Nicolino M, van der Ploeg A. Diagnostic challenges for Pompe disease: an under-recognized cause of floppy baby syndrome. Genitourin Med. 2006;8:289–96.
39. Kroos M, Pomponio RJ, van Vliet L, Palmer RE, Phipps M, Van der Helm R, Halley D, Reuser A. Update of the Pompe disease mutation database with 107 sequence variants and a format for severity rating. Hum Mutat. 2008;29:E13–26.
40. Sivasankaran S. Restrictive cardiomyopathy in India: the story of a vanishing mystery. Heart. 2009;95:9–14.
41. Mocumbi AO, Ferreira MB, Sidi D, Yacoub MH. A population study of endomyocardial fibrosis in a rural area of Mozambique. N Engl J Med. 2008;359:43–9.
42. Gleich GJ, Leiferman KM. Hypereosinophilic syndromes: current concepts and treatments. Br J Haematol. 2009;145:271–85.
43. Rioux JD, Stone VA, Daly MJ, Cargill M, Green T, Nguyen H, Nutman T, Zimmerman PA, Tucker MA, Hudson T, Goldstein AM, Lander E, Lin AY. Familial eosinophilia maps to the cytokine gene cluster on human chromosomal region 5q31-q33. Am J Hum Genet. 1998;63:1086–94.
44. Kleinfeldt T, Ince H, Nienaber CA. Hypereosinophilic syndrome: a rare case of Loeffler's endocarditis documented in cardiac MRI. Int J Cardiol. 2009;15.