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Restrictive cardiomyopathy: definition and diagnosis

Claudio Rapezzi[1,2]*, Alberto Aimo [3,4], Andrea Barison [3,4], Michele Emdin[3,4], Aldostefano Porcari[5], Ales Linhart [6], Andre Keren [7,8], Marco Merlo [5], and Gianfranco Sinagra[5]

[1]Cardiologic Centre, University of Ferrara, Via Savonarola, 9, 44121 Ferrara, Italy; [2]Maria Cecilia Hospital, GVM Care & Research, Via Corriera, 1, 48033 Cotignola, Ravenna, Italy; [3]Health Science Interdisciplinary Center, Scuola Superiore Sant'Anna, piazza Martiri della Libertà 33, 56127 Pisa, Italy; [4]Cardiology Division, Fondazione Toscana Gabriele Monasterio, via Moruzzi 1, 56124 Pisa, Italy; [5]Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart-ERN GUARD-Heart, Via Giacomo Puccini, 50, 34148 Trieste, Italy; [6]General University Hospital and Charles University, Opletalova 38, 110 00 Staré Město, Czech Republic; [7]Cardiology Division, Hadassah Hebrew University Hospital, Sderot Churchill 8, Jerusalem, Israel; and [8]Heart Failure Center, Clalit Health Services, Bnei Brit St 22, Jerusalem, Israel

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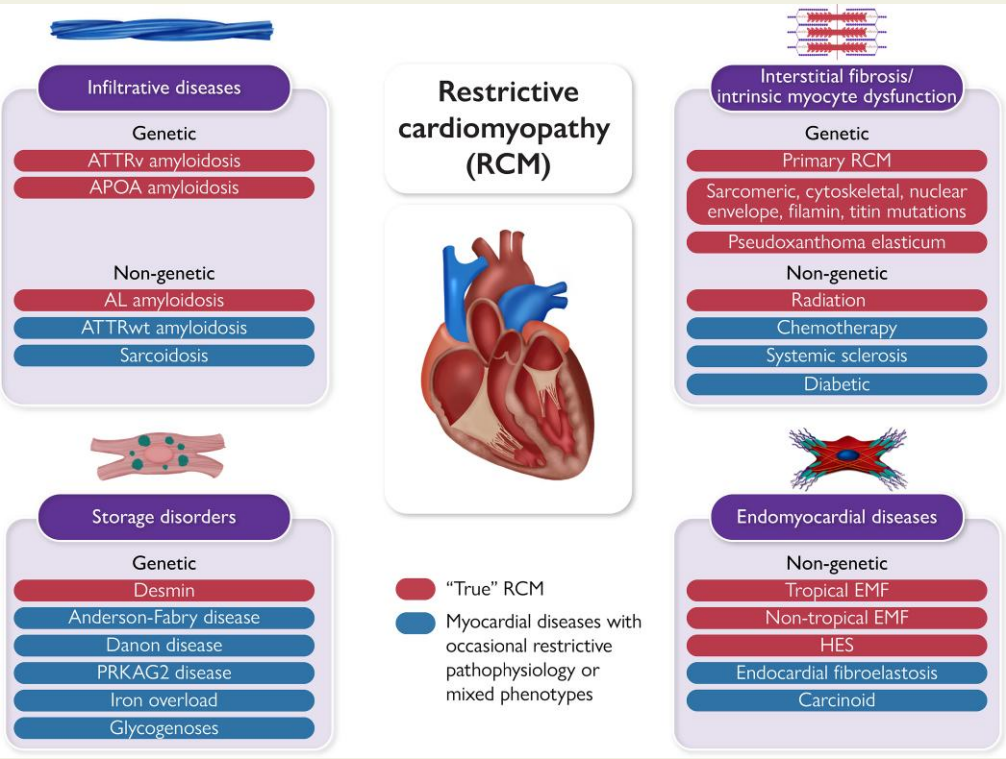
Graphical Abstract



Proposed classification of restrictive cardiomyopathy according to myocardial histology, the genetic basis and the transient or permanent nature of restriction. APOA, apolipoprotein A; ATTRv, variant amyloid transthyretin amyloidosis; EMF, endomyocardial fibrosis; HES, hypereosinophilic syndrome; PRKAG2, protein kinase AMP-activated non-catalytic subunit gamma 2.

* Corresponding author. Tel: +39 0532239882, Fax: +39 0532 293031, Email: claudio.rapezzi@unife.it

Abstract

Restrictive cardiomyopathy (RCM) is a heterogeneous group of diseases characterized by restrictive left ventricular pathophysiology, i.e. a rapid rise in ventricular pressure with only small increases in filling volume due to increased myocardial stiffness. More precisely, 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. Beyond this shared haemodynamic hallmark, the phenotypic spectrum of RCM is wide. 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. 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). Furthermore, elements of both hypertrophic and restrictive phenotypes may coexist in some patients, making the classification challenge. Restrictive pathophysiology can be demonstrated by cardiac catheterization or Doppler echocardiography. The specific conditions may usually be diagnosed based on clinical data, 12-lead electrocardiogram, echocardiography, nuclear medicine, or cardiovascular magnetic resonance, but further investigations may be needed, up to endomyocardial biopsy and genetic evaluation. The spectrum of therapies is also wide and heterogeneous, but disease-modifying treatments are available only for cardiac amyloidosis and, partially, for iron overload cardiomyopathy.

Keywords Restrictive cardiomyopathy • RCM • Classification • Myocardial disease • Amyloidosis

Restrictive cardiomyopathy (RCM) has been considered the least common form of heart muscle disease, and also the one most difficult to define and classify, encompassing a group of disorders whose classification and diagnosis pose unique challenges. Restrictive cardiomyopathy is undoubtedly the cardiomyopathy with the widest spectrum of aetiologies and histological features and the one most often requiring cardiac catheterization or endomyocardial biopsy (EMB) to achieve a definite diagnosis. To add further complexity, the boundaries of RCM are becoming increasingly blurred because many disease-causing genes are shared with other cardiomyopathies, and cardiac phenotypes may change over time. Although the haemodynamic definition of restrictive pathophysiology is undisputable, the pressure-volume relations can vary, and the cut-offs to diagnose restriction are not unequivocal. Moreover, novel imaging techniques including cardiovascular magnetic resonance (CMR), scintigraphy with bone tracers, and positron emission tomography help to establish specific causes of tissue damage (e.g. amyloidosis, Anderson–Fabry disease, haemochromatosis, sarcoidosis), even when typical restrictive pathophysiology has not fully developed yet.

Definition of restrictive cardiomyopathy

All classification systems serve two main purposes:(i) to provide nosographic schemes where disorders are classified according to their specific features;(ii) to suggest criteria that help the diagnostic workup. Rarely is a single classification scheme fully functional for both purposes. The classification of cardiomyopathies proposed by the European Society of Cardiology (ESC) position statement(2008) (i) has been widely accepted by the cardiological community because it is easily applicable in clinical practice and immediately translates into a diagnostic algorithm. This classification system requires to assess the cardiac phenotype (first of all through transthoracic echocardiogram), to search for family history of the disease (and then a possible genetic basis), and to reach the final specific diagnosis (*Figure 1*). Although this probably remains the best classification system to categorize cardiomyopathies, it may be suboptimal when applied to RCM. First, hypertrophic, dilated, and many cases of arrhythmogenic cardiomyopathy share morphological and/or functional characteristics that are easily identifiable through a routine echocardiogram. Conversely, the main unifying feature of RCM is strictly haemodynamic and consequently not immediately evident on the echocardiogram. Restrictive left ventricular (LV) physiology is produced by an increased myocardial stiffness, causing a rapid rise in ventricular pressure at the beginning of the diastolic phase with only small increases in filling volumes or a critical reduction of ventricular volumes up to a near obliteration, caused by massive wall hypertrophy or endomyocardial proliferation.[1] According to the ESC definition, the other features of RCM are 'normal or reduced systolic and diastolic volumes (of one or both ventricles)' and 'normal ventricular wall thickness'.[1] While this definition is conceptually accurate, its literal interpretation would lead to the exclusion of many disorders with a common restrictive physiology, including several forms of RCM listed in the same document (*Table 1*).

Four main violations of ESC diagnostic criteria should be admitted:

(1) LV (and eventually right ventricle, RV) wall thickness is increased in many conditions due to: (i) cardiomyocyte hypertrophy, (ii) interstitial infiltration [as in cardiac amyloidosis (CA)], (iii) intracellular storage (as in glycogenosis, haemochromatosis, or sphingolipidoses).
(2) A restrictive physiology may be found either at an early stage (possibly evolving to a hypokinetic and dilated phenotype) or at an advanced stage (often preceded by a hypertrophic phenotype). This is the case of iron-overload cardiomyopathy and cardiac sarcoidosis, which can display a restrictive physiology in an initial phase, while overt cardiac disease has a hypokinetic and dilated phenotype.
(3) The presence of a restrictive LV physiology does not always imply an RCM. A restrictive pathophysiology may develop at the end stage of any type of cardiomyopathy. The restrictive diastolic filling may be transiently identified in cardiomyopathies, such as hypertrophic or dilated cardiomyopathy (HCM/DCM) in the presence of severe congestion and disappear following optimization of fluid balance.

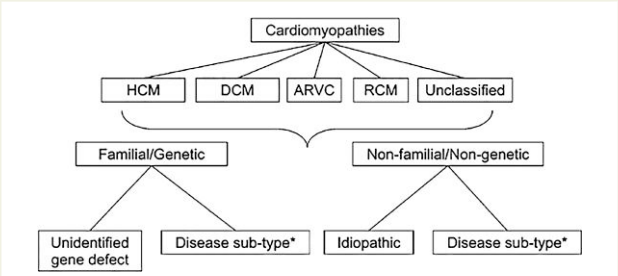


Figure 1 Classification of cardiomyopathies according to the 2008 European Society of Cardiology position statement. ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy. Reprinted with permission from: Elliott *et al.*[1]

(4) The evolution of the phenotypes over time is not considered in the ESC classification. Although restrictive pathophysiology is the essence of RCMs, some primitive, genetically determined DCMs with mild or no ventricular dilatation and HCMs without significant hypertrophy may initially present with restrictive physiology,[2] but they behave and evolve as DCMs and HCMs and should be considered and treated accordingly. An HCM with systolic dysfunction approaching the late stage of disease that develops a restrictive filling pattern poses a diagnostic dilemma between RCM and HCM, depending on the stage of disease. It could manifest as RCM if encountered at the end-stage of the natural history with ventricular wall thinning, systolic dysfunction, and restrictive filling pattern. However, if diagnosed in non-advanced stages, it is considered a 'characteristic' HCM that eventually develops systolic dysfunction and restrictive pathophysiology as the cardiomyopathic process progresses. Cardiac amyloidosis is traditionally considered the paradigm of RCM, but a restrictive filing pattern might be variably present. Cardiac amyloidosis caused by amyloid light-chain (AL) amyloidosis may be present at an early stage, with mild or absent ventricular wall thickening with restrictive pathophysiology, regressing following effective chemotherapy.[3] Conversely, CA due to transthyretin (ATTR) amyloidosis may present with mild diastolic dysfunction and develop a restrictive filling pattern in later stages when significant LV wall thickening develops.[4]

Proposal for a new definition and classification of restrictive cardiomyopathy

The approach we followed was first of all to refine and enhance the nosographic aspect of the classification and, subsequently, to provide useful insights for the diagnosis of individual diseases. The definition of RCM can be slightly modified as follows: RCM is characterized by the coexistence of persistent restrictive pathophysiology, commonly with atrial dilatation, and nondilated ventricles, regardless of ventricular wall thickness and systolic function. Several forms of RCM are predominantly due to endocardial involvement, leading to a similar haemodynamic patterns as for isolated myocardial diseases.

Table 1 Causes of restrictive cardiomyopathy listed in the 2008 European Society of Cardiology document

Familial	Non-familial
Familial, unknown gene	Amyloid (AL/prealbumin)
Sarcomeric protein mutations	Scleroderma
Troponin I (RCM ± HCM)	Endomyocardial fibrosis
Essential light chain of myosin	Hypereosinophilic syndrome
Familial amyloidosis	Idiopathic
Transthyretin (RCM + neuropathy)	Chromosomal cause
Apolipoprotein (RCM + nephropathy)	Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan)
Desminopathy	
Pseuxanthoma elasticum	Carcinoid heart disease
Haemochromatosis	Metastatic cancers
Anderson–Fabry disease	Radiation
Glycogen storage disease	Drugs (anthracyclines)

AL, amyloid light-chain; HCM, hypertrophic cardiomyopathy.
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The ESC classification system does not consider the myocardial substrate, which is extremely heterogeneous (*Figure 2*). Indeed, the histological abnormalities may involve the endocardium and/or the myocardium, and myocardial disorders may affect either the interstitial space or cardiomyocytes. Some cases even lack gross morphological abnormalities because the problem lies in cardiomyocyte functioning.

The classification of RCM could then be usefully implemented by consideration of the histological substrate, either through tissue sampling examination or, non-invasively, through CMR and/or nuclear medicine, the latter with regard to CA. From a conceptual standpoint, including the histological substrate in the classification scheme is relevant but does not represent a mandatory initial step of the diagnostic workup.

Other levels of classification concern the differentiation between familial/genetic and non-familial/non-genetic forms, and between disorders characterized by transient or permanent restriction (*Graphical Abstract*).

The restrictive phenotype: haemodynamic, clinical and imaging features

Patients with RCM have a rigid, noncompliant LV with impaired diastolic filling and high filling pressures. Chronically elevated LV diastolic pressures commonly induce pulmonary hypertension, which tends to exacerbate right heart failure (HF), especially when the RV is affected by the disease process, as in CA. In the early stages of RCM, LV systolic function is typically preserved, at least when assessed in terms of LV ejection fraction (LVEF), but tends to deteriorate over time. The longitudinal systolic function of the LV is frequently reduced in the early

phases, particularly in CA. Despite preserved LVEF, the LV cannot fill adequately and, furthermore, ventricular cavity size can be reduced in presence of severely increased wall thickness, resulting in an almost fixed stroke volume. Under these conditions, the only adaptive response to exercise able to increase cardiac output is the increase in heart rate, which may be blunted in patients with associated autonomic dysfunction, amplifying the risk of hypotension during exercise. Furthermore, atrial remodelling and dilatation often lead to atrial fibrillation (AF), which reduces atrial contribution to LV filling.[5]

By invasive haemodynamic assessment, RCM is characterized by elevated diastolic filling pressures and a rapid equalization of filling pressures of the four cardiac chambers during diastole, with a frequent 'dip and plateau' or 'square root' pattern on pressure tracings (*Figure 3*). This pattern becomes more evident with manoeuvres that augment ventricular filling, such as volume infusion or leg raising. Although many of these findings are shared by constrictive pericarditis (CP), there are many differences between these two conditions. For example, atrial *x* and *y* descents tend to be relatively blunted in RCM compared with CP, and a wave may be depressed when the atria are primarily affected (as in CA). Disproportionate left heart stiffness may result in moderate pulmonary hypertension, which is rarer and milder in CP. Furthermore, the RCM process renders the chambers minimally distensible; therefore, there is little respiratory variation in flow or pressure, as opposed to CP. Ventricular interdependence is minimal in RCM, therefore there is little change in peak ventricular systolic pressures with respiration and they move in the same direction.[5,6]

This haemodynamic profile shared by all forms of RCM can be characterized quite accurately by a transthoracic echocardiogram. The first clue of restrictive pathophysiology is the combination of biatrial enlargement (which cannot be attributed to specific causes such as valve disease or AF), normal or mildly reduced LV and RV ejection fraction and non-dilated ventricles. Doppler imaging can then show a restrictive filling pattern of transmitral flow with increased early diastolic filling velocity (E wave) due to elevated left atrium (LA) pressure, and decreased atrial filling velocity (A wave) due to the high ventricular diastolic pressure, reduction of mitral deceleration time, and isovolumetric relaxation time. Additionally, the ratio between systolic and diastolic pulmonary venous flow ratios is markedly reduced because of high LA pressures. Tissue Doppler typically shows reduced early diastolic myocardial velocity (e′) leading to an elevated *E*/e′ ratio (*Figure 4*). Congestion of the inferior vena cava and hepatic veins and diastolic flow reversal in the hepatic veins during inspiration are common, following the inability of a non-compliant RV to accommodate the increased venous return.[6,8,9]

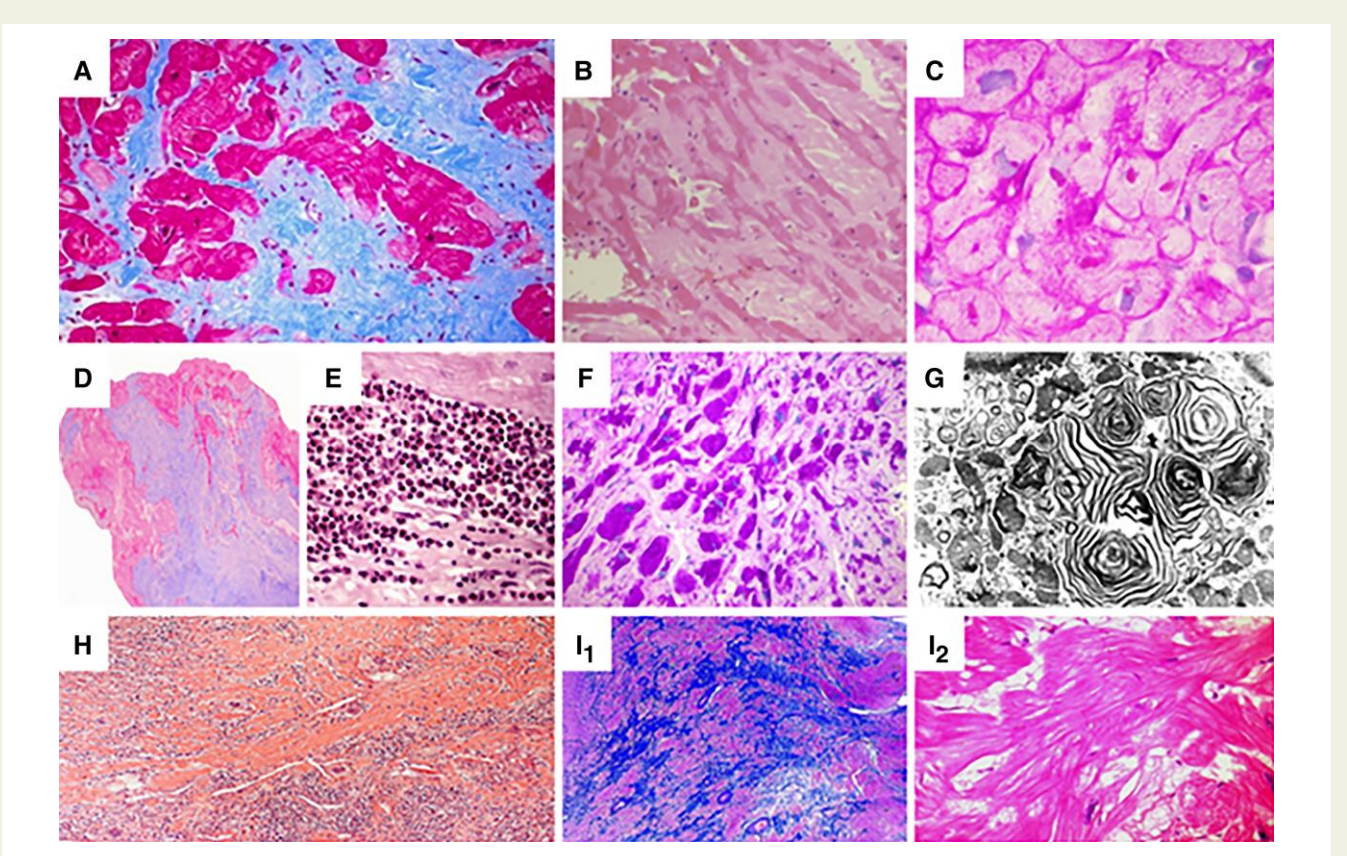

Figure 2 Myocardial tissue in nine different forms of restrictive cardiomyopathy (*A*) idiopathic restrictive cardiomyopathy; (*B*) cardiac amyloidosis (with enlargement of the extracellular spaces by amyloid fibres); (*C*) Danon disease (with intracellular glycogen deposits); (*D*) endomyocardial fibrosis (with extensive fibrosis in the endocardium and myocardium); (*E*) hypereosinophilic syndrome (with tissue accumulation of eosinophils); (*F*) glycogenosis (with tissue accumulation of glycogen); (*G*) Anderson–Fabry disease (with lipid deposits as seen through electron microscopy); (*H*) sarcoidosis (with tissue granulomas); (*I*) end-stage hypertrophic cardiomyopathy (with extensive fibrosis). Courtesy of Dr Ornella Leone, Bologna, Italy.

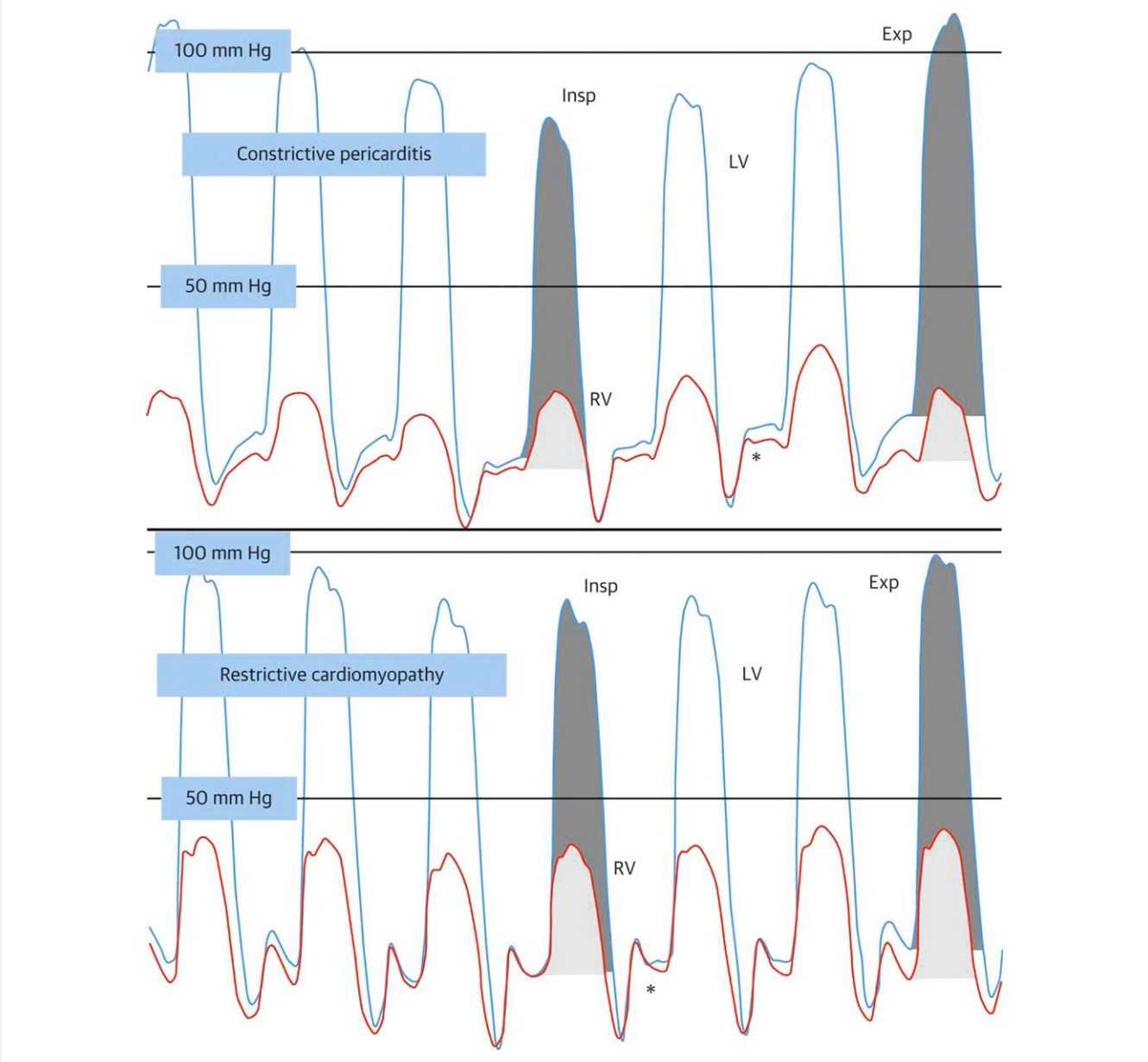

Figure 3 Simultaneous right and left ventricular haemodynamic assessment in constrictive pericarditis and restrictive cardiomyopathy. (*Top*) Left ventricular (*blue*) and right ventricular (*orange*) hemodynamic pressure tracings in constrictive pericarditis. End-diastolic filling pressures are elevated, and a 'square root' sign is present on both tracings (*). Enhanced ventricular interdependence is present, demonstrated by visualization of the systolic area index, right ventricular (*light grey*) and left ventricular (*dark grey*) areas under the curve for both inspiration (*Insp*) and expiration (*Exp*). During inspiration, there is an increase in the area of the right ventricular pressure curve and a decrease in the area of the left ventricular pressure curve. (*Bottom*) left ventricular and right ventricular pressure tracings in restrictive cardiomyopathy. End-diastolic pressures are elevated and a square root sign (*) is seen; there is no evidence of enhanced ventricular interdependence, with parallel changes in LV and RV pressure curve areas. Reprinted with permission from Geske *et al.*[7]

The characteristic alterations of each disorder are superimposed on this common morphological and functional phenotype, leading to a highly heterogeneous picture. Cardiovascular magnetic resonance and myocardial histology allow to investigate the extremely heterogeneous myocardial substrate. Even the electrocardiographic picture may differ widely across the spectrum of RCM. A possible specific marker of RCM, albeit not sensitive, is the evidence of marked biatrial enlargement. The clinical picture of RCM may be highly variable. Heart failure and AF are still the most common findings. Heart failure is most often right-sided or biventricular, with liver enlargement, lower limb oedema, and ascites.

General principles of treatment

Three characteristics of RCM pathophysiology are particularly relevant and influence the therapeutic strategy:

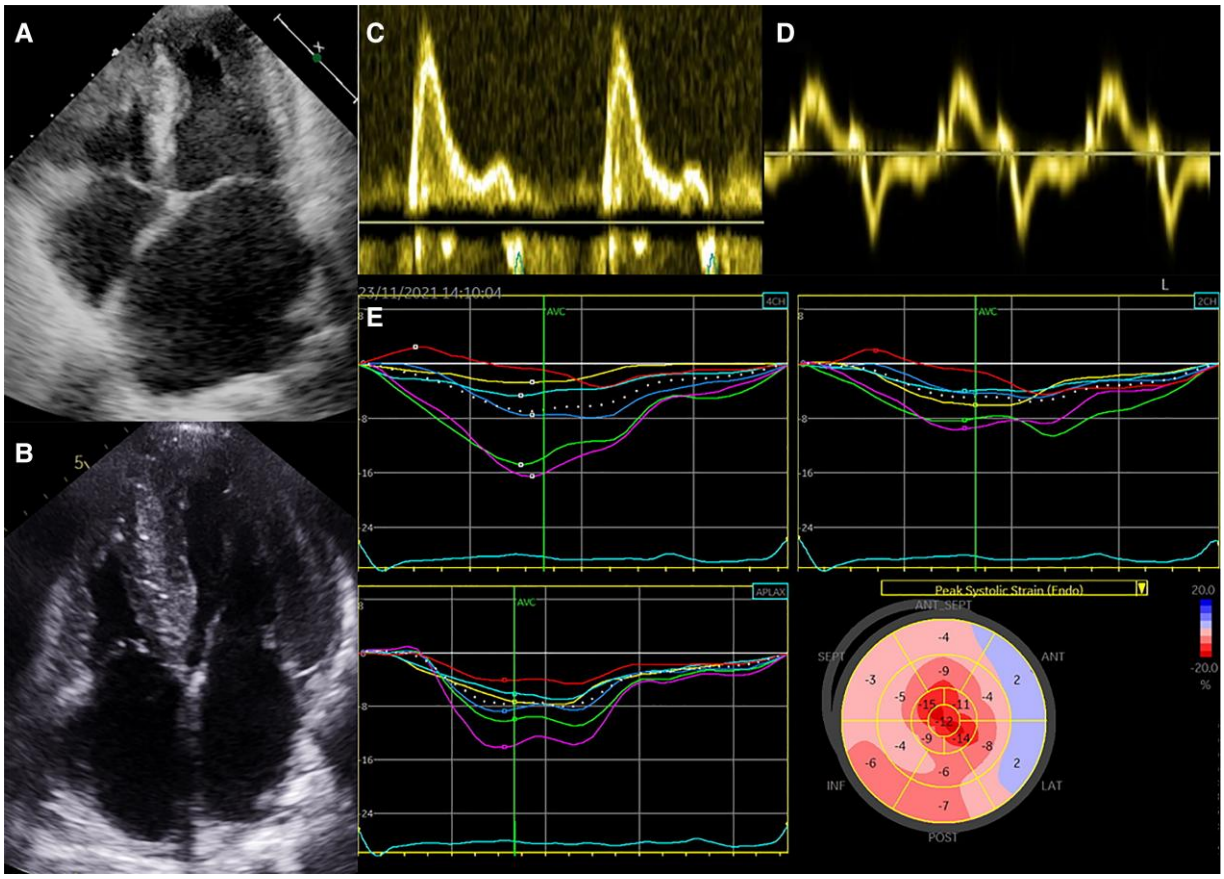

Figure 4 Echocardiography in restrictive cardiomyopathies. (*A*) Small left ventricular cavity size in presence of significantly increased wall thickness and severe left atrial dilatation; (*B*) biventricular wall thickening in absence of pulmonary hypertension; (*C* and *D*) restrictive filling pattern with elevated *E*/*E*′ ratio in keeping with increased left ventricular filling pressures; (*E*) myocardial strain analysis showing an apical sparing pattern in a patient with cardiac amyloidosis.

- The duration of diastole and the increased filling pressure have a relatively limited impact on the amount of ventricular filling, so that stroke volume is virtually fixed and cardiac output is crucially dependent on heart rate change.
- Reverse remodelling (i.e. the reduction in LV volumes and LVEF recovery) is not a therapeutic goal. On the contrary, the clinical improvement may be accompanied by a small increase in LV end-diastolic volume and stroke volume.[10]
- Beta-blockades may not be tolerated due to their negative chronotropic and, to a lesser extent, inotropic impact.

Relieving congestion is the first goal. Loop diuretics reduce pulmonary and peripheral oedema and ascites. Forcing diuresis should be avoided because even mild hypovolaemia may cause a fall in stroke volume and cardiac output. In cases with overtly restrictive physiology, the strict dependence of cardiac output on the heart rate implies that beta-blockers may worsen the haemodynamic function and induce hypotension. Patients are typically poorly tolerant of bradycardia, and bradyarrhythmias may require the implantation of an atrioventricular sequential pacemaker. Drugs acting on the renin-angiotensin-aldosterone system have not demonstrated prognostic benefit and may be poorly tolerated because of hypotension.[11] Atrial fibrillation is common and often poorly tolerated because of the loss of atrial contribution to ventricular filling. Rhythm control should be preferred over rate control, but achieving and maintaining sinus rhythm may be difficult. Patients with CA and AF have a very high thromboembolic risk and should be anticoagulated regardless of their CHA_2DS_2-VASc score. The same approach should be evaluated in other types of RCM. Implantation of a ventricular assist device is challenging because the LV cavity may be very small and the standard route of inflow cannulation of the LV apex carries a significant risk of obstruction.[12] Heart transplantation may be considered in selected patients with similar results as in other HF aetiologies, except for CA and radiation-induced cardiomyopathy, where results are usually less satisfactory.[13] Interestingly, in recent years characterized by earlier recognition and management of CA, heart transplantation has been proposed as an effective therapeutic option in carefully selected patients with CA, with outcomes similar to those transplanted for other causes of HF,[14] when the underlying disease is successfully treated. The management of anaesthesia before transplantation may be challenging. The general principles of peri-operative management are: to keep adequate filling pressures, to maintain sinus rhythm whenever possible, to manage electrolyte disturbances, and to control systemic vascular resistance in the presence of relatively fixed cardiac output. Finally, disease-modifying therapies targeting specific proteins or nucleic acids have recently become available for some forms of RCM.

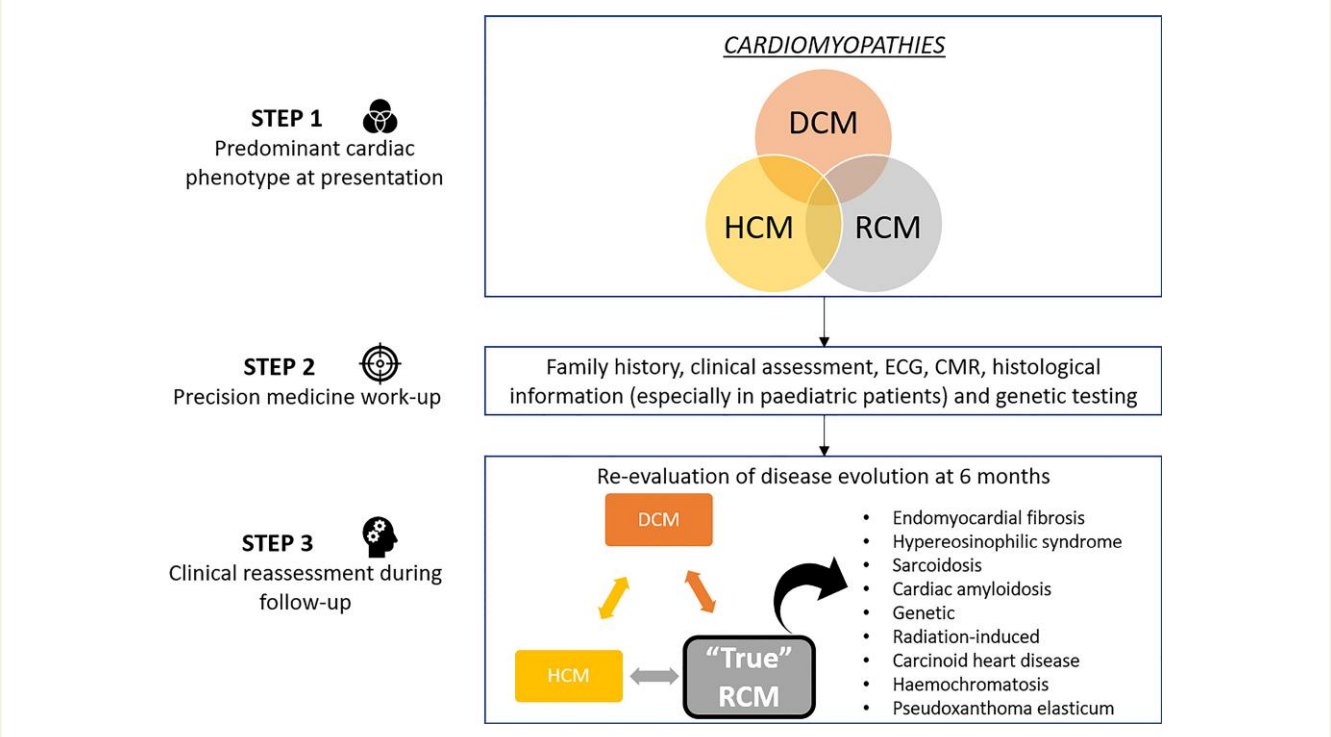

Figure 5 Proposed flowchart for contemporary diagnostic work-up of restrictive cardiomyopathy. CMR, cardiovascular magnetic resonance; DCM, dilated cardiomyopathy; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy.

Recent advances in diagnostic standards and disease-modifying therapies of the most common forms of restrictive cardiomyopathy

Infiltrative diseases

Cardiac amyloidosis is the prototype of infiltrative diseases. One of more than 30 different precursor proteins with an unstable tertiary structure misfolds and aggregates into amyloid fibrils that accumulate in the extracellular space of organs and tissues, including the heart.[15] Over 95% of cases of cardiac involvement are due to AL- or ATTR-CA.[16,17] Amyloid light-chain amyloidosis results from the deposition of immunoglobulin light-chains from a plasma cell dyscrasia. Transthyretin (TTR) is a protein synthetized in the liver that circulates as a tetramer transporting thyroxin and retinol. Transthyretin may dissociate into monomers and deposits as amyloid fibrils in organ tissues, either because of mutations that reduce the stability of TTR tetramers (variant ATTR, ATTRv) or as an age-related phenomenon (wild-type ATTR, ATTRwt). Infiltration of ventricular walls produces a typical pseudo-hypertrophy with non-dilated or small ventricles. The LV mass increase is often symmetrical in AL-CA and, initially, asymmetric with predominantly septal hypertrophy in ATTR-CA. A base-to-apex gradient in LV myocardial infiltration may explain the preserved contractility of the apex on strain analysis. Diastolic dysfunction is almost invariably present and progressive.[4] Atrial involvement manifests with atrial dysfunction and an increased risk of AF. Conduction system disease may manifest with varying degrees of heart block and bundle branch block.[18] Atrioventricular valves are often thickened. Pericardial involvement can lead to small pericardial effusions, while large effusions are rare.[19] Restrictive pathophysiology is typical of the overt disease and may be absent or mild in the early stages. The progressive increase in parietal and chamber stiffness leads to an increase in LV pressures for the same LV volumes and concomitant declines in stroke volume, cardiac output, and, frequently, blood pressure. The parallel decrease in stroke volume and end-diastolic volume explains why LVEF remains preserved until the late phases. Nonetheless, myocardial contractility, chronotropic competence, and inotropic reserve during exercise are reduced in almost all patients even while LVEF is still preserved.[19]

Treatment of CA must relieve HF symptoms and target the underlying disease. Loop diuretics are the mainstay of HF management. Mineralocorticoid receptor antagonists are generally well tolerated. Beta-blockers have no proven benefit and may be poorly tolerated when cardiac output is dependent on heart rate because of a low, fixed stroke volume. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may induce hypotension, especially in patients with polyneuropathy (PN). However, further prospective studies are warranted since patients with CA have greater neurohormonal activation than those with non-amyloidotic HF,[20] and neurohormonal antagonist drugs in recent retrospective reports have been found to be safe and well tolerated, though beta-blocker therapy is less tolerated in patients with AL amyloidosis and/or worse haemodynamic function.[21,22]

Disease-modifying treatment for AL amyloidosis targets the underlying clone. In around one-fifth of patients, autologous stem cell transplantation can be considered as an upfront treatment or

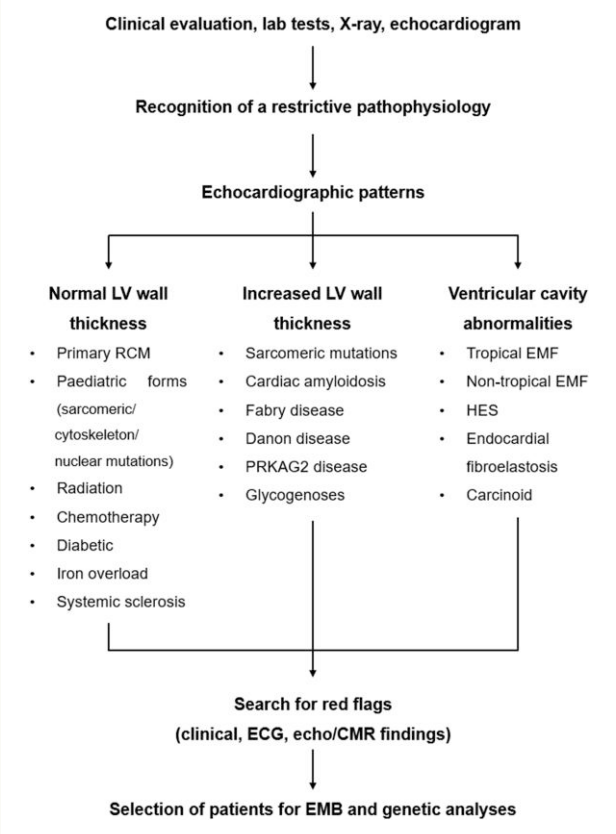

Figure 6 Red flag-based diagnostic approach. The main disorders presenting with normal or increased left ventricular wall thickness are listed. CMR, cardiovascular magnetic resonance; EMB, endomyocardial biopsy; EMF, endomyocardial fibrosis; HES, hypereosinophilic syndrome; LV, left ventricle; PRKAG2, protein kinase AMP-activated non-catalytic subunit gamma-2; RCM, restrictive cardiomyopathy.

following bortezomib-based conditioning. Bortezomib can improve the depth of response after transplantation and is the backbone of treatment for patients not eligible for transplantation.[23] The combination of daratumumab, bortezomib, cyclophosphamide, and dexamethasone recently emerged as an effective therapy for patients not eligible for transplantation. The treatment goal is to achieve an early and profound haematologic response and an organ response in the long term.[23]

Treatments acting on several steps of the amyloidogenic cascade of ATTR-CA are available. Tafamidis stabilizes the TTR tetramer and may thus reduce the formation of TTR amyloid. It prolongs survival in patients with ATTR-CA[10,24] and is the only approved treatment for patients with ATTRwt-CA or ATTRv-CA without PN.[25–29] Tafamidis treatment has received a Class I, level of evidence B recommendation for patients with ATTR-CA and New York Heart Association Classes I and II.[30]

The small interfering RNA (siRNA) patisiran and the antisense oligonucleotide (ASO) inotersen have been approved for the treatment of patients with Stage 1 and 2 ATTRv PN,[26,31] with some evidence of positive effects on cardiac morphology and function in patients with CA.[32] Patisiran is administered by intravenous infusion once every 3 weeks and is usually well tolerated. Inotersen is administered as one subcutaneous injection once per week; glomerulonephritis and low platelet count are the most feared adverse events. Patients on patisiran or inotersen should receive vitamin A supplementation.[31] New formulations of siRNA and ASO and the blockade of TTR production by genome editing are being investigated.

Cardiac sarcoidosis, often included among RCMs, is a multi-system inflammatory disorder of unknown aetiology characterized by the formation of non-caseating granulomas. The disease evolves toward ventricular dilatation and hypokinesia but can initially display a restrictive physiology in a ventricle with regional contractile abnormalities. Cardiac involvement is almost always associated with lung disease, but the absence of overt lung disease should not exclude cardiac sarcoidosis.[33] The proposed diagnostic criteria refer to cardiac sarcoidosis with a dilated and hypokinetic phenotype.[33] Immunosuppression with corticosteroids remains the standard therapy for the acute inflammatory phase, but steroid-sparing agents are being increasingly used. Patients with cardiac sarcoidosis should also receive guideline-directed therapies for HF and arrhythmias.[34]

Interstitial fibrosis/intrinsic myocyte dysfunction

Primary RCMs include idiopathic and genetic RCMs. In idiopathic forms, familial aggregation or the absence of any identifiable cause may suggest a genetic disorder, but the search for gene mutations is negative. Familial cases generally display a pattern of autosomal dominant inheritance with variable penetrance. Mutations have been described in several genes encoding sarcomeric and non-sarcomeric proteins. In both idiopathic and genetic RCMs, disease mechanisms likely include abnormal functioning of sarcomere proteins and the activation of fibrotic pathways following tissue damage.[6,34,35] Most patients are diagnosed at paediatric age due to severe chronic HF. Skeletal myopathy and atrioventricular block are present in some familial cases. Considerable genotypic and phenotypic overlap exists between restrictive RCM and HCM. The two different phenotypes can be expressed by the same mutations; in a number of cases, the phenotype is mixed from the beginning (overtly restrictive haemodynamics with generally modestly increased LV mass); in others, there is an evolution from classical HCM to RCM. HCM associated with thin-filament mutations is characterized by less prominent and atypically distributed hypertrophy, increased fibrosis, and more adverse remodelling (hypokinetic or restrictive evolution), leading to congestive symptoms and more severe diastolic dysfunction, compared with thick-filament HCM.[2] Preclinical studies[36,37] using transgenic mouse lines with thin-filament genes demonstrated a markedly increased myofilament calcium sensitivity, leading to development of restrictive diastolic patterns and systolic dysfunction over time. The early impairment in excitation-contraction coupling, energetic derangement, abnormal cardiomyocyte signalling, and intrinsic abnormalities of sarcomere relaxation caused by thin-filament mutations may drive progressive remodelling at the cellular and extracellular levels,[38] resulting in impaired contractile and relaxation properties of the myocardium. No disease-modifying therapy is currently available.

Pseudoxanthoma elasticum is an inherited systemic disease of connective tissue transmitted in an autosomal recessive manner and caused by mutations in the *ABCC6* gene. Histology of affected tissues exhibits elastic fibre mineralization and fragmentation. Restrictive cardiomyopathy in relation to diffuse endocardial fibroelastosis is very rare.[39] No approved treatment exists.

Changes in radiation dose and delivery have reduced the incidence of cardiac complications following ***radiation therapy***, but the risk of

Table 2 Examples of signs, symptoms and routine laboratory tests that raise the suspicion of specific aetiologies

	Red flag	Possible disease
Age	Paediatric	Primary RCM, EFE, Danon disease, hereditary haemochromatosis
	Young age	Sarcomeric, nuclear, cytoskeletal, desmin, titin mutations, iron overload,
	Adulthood or old age	desminopathy, AL amyloidosis, ATTRv amyloidosis, ATTRwt amyloidosis
Familiarity/ inheritance	Autosomal dominant	ATTRv amyloidosis, primary RCM, desminopathy
	Autosomal recessive	Pseudoxantoma elasticum, hereditary hemochromatosis, desminopathy
	X-linked	Anderson-Fabry disease, Danon disease
	Maternal	Mitochondrial disease
Physical examination	Ruptured biceps, carpal tunnel syndrome, spinal stenosis	ATTR-CA
	Skin pigmentation, hypogonadism, arthropathy, liver cirrhosis, skin bronzing, diabetes	Haemochromatosis
	Skin lesions (angiokeratomas)	Anderson–Fabry disease
	Peripheral muscle weakness	Danon disease, desminopathy
	Intellectual deficit	Danon disease
ECG	Short PR interval	Anderson–Fabry disease
	Preexcitation	Danon disease, PRKAG2
	A-V block	Advanced Anderson–Fabry disease
	Extremely high QRS voltages	Danon disease
	Short PR interval and RBBB	Anderson–Fabry disease
	Low QRS voltages	Cardiac amyloidosis, end-stage HCM
	Disproportion between QRS voltages and LV wall thickness	Cardiac amyloidosis
	Pseudo-infarct QRS pattern	Cardiac amyloidosis
Routine laboratory tests	↑ creatine kinase	Desmin, lamin, myofibrillar myopathies
	↑ transferrin saturation/hyperferritinaemia	Haemochromatosis
	Proteinuria, increased free light chain, reduced GFR	AL amyloidosis
	Eosinophilia	Endomyocardial disorders and hypereosinophilic syndrome

AL, amyloid light-chain; ATTR, amyloid transthyretin (v, variant; wt, wild-type); AV, atrioventricular; CA, cardiac amyloidosis; EFE, endocardial fibroelastosis; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; LV, left ventricle; RCM, restrictive cardiomyopathy.

contemporary regimens remains unknown, also because of the lack of standardized echocardiographic screening and the often long latent period.[40] At sufficient doses, radiation of the mediastinum can damage virtually any component of the heart. Indeed, patients often display a combination of cardiomyopathy, valve disease, pericardial disease, and coronary artery disease. Radiation-related RCM is due to early inflammation, microvascular injury, and reduced capillary density, which lead to ischaemia and myocyte replacement with diffuse bands of collagen replacement fibrosis.[41] Radiation predominantly causes RCM with diastolic dysfunction, usually with a latency of 10–15 years.[42] Discriminating RCM from CP may also be difficult because these conditions may coexist. Clinical management of established disease is symptomatic and consists largely of diuretics to control volume overload.[43]

Endomyocardial disorders

Endomyocardial fibrosis (EMF) and hypereosinophilic syndrome (HES) are characterized by diffuse thickening of the LV endocardium secondary to the proteotoxic damage produced by eosinophils and the ensuing proliferation of fibrous and elastic tissue. The LV is invariably involved, often together with the mitral and aortic valves. Isolated right ventricular involvement may rarely occur.[44,45] Endomyocardial fibrosis is commonly seen in equatorial countries and accounts for ~20% of HF cases and 15% of cardiac deaths in equatorial Africa. A combination of dietary, environmental, and infectious factors may elicit an inflammatory process leading to progressive endomyocardial damage and scarring. The natural history of EMF includes an active phase with inflammation and eosinophilia that progresses to restrictive heart disease.[45] Hypereosinophilic syndrome affecting the heart, formerly known as Loeffler's endocarditis, is a very rare condition caused by the release of highly active biological substances that damage the endothelium and myocardium. Most patients are diagnosed between 20 and 50 years of age. Mechanisms of eosinophilia include helminthic and parasitic infections, malignancies, eosinophilic leukaemia, allergic drug reactions, hypersensitivity, and eosinophilic granulomatosis with polyangiitis. The fibrotic stage results in RCM due to extensive endomyocardial fibrosis and resembles EMF.[45]

Endocardial fibroelastosis (EFE) is characterized by diffuse thickening of the LV endocardium secondary to proliferation of fibrous and elastic tissue. Two forms have been described: a dilated form (DCM phenotype), in which the LV is enlarged, and a 'contracted' form (RCM phenotype), in which the LV cavity is small.[43] A familial pattern is seen in the majority, with presentation commonly occuring during infancy. Mitral and aortic valves are frequently involved. Isolated RV involvement may rarely occur. The 'contracted' form produces restrictive haemodynamics and a clinical picture of left-sided obstructive disease, particularly if the mitral valve is involved. Endocardial fibroelastosis is

Table 3 Main cardiovascular magnetic resonance findings in restrictive cardiomyopathies

Disease	Wall thickness	Hypertrophy pattern	RV involvement	LVEDV	LVEF	LGE pattern	Native T1	ECV	T2 mapping	Atrial enlargement
Cardiac amyloidosis	↑↑	Asymmetrical (ATTR) Symmetrical (AL)	+	~/↓	~/↓	Diffuse subendocardial/transmural	↑↑	↑↑	↑/~	+
IOC	↑/~	Symmetrical	+	↑/~	~/↓	Not frequent, insertion point or rarely diffuse	→	↑/~	~/↑	+/–
EMF/EFE/HES	↑/~	Apical	++	↓	↓	Diffuse subendocardial	↑/~	↑/~	↑/~	+
Anderson/Fabry disease	↑↑ (M) ↑(W)	Symmetrical	+	↓/~	~/↑	Midwall basal inferolateral wall	→	↓/~	↓/~	+/–

AL, amyloid light-chain; ATTR, amyloid transthyretin; ECV, extracellular volume; EFE, endocardial fibroelastosis; EMF, endomyocardial fibrosis; HES, hypereosinophilic syndrome; IOC, iron overload cardiomyopathy; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; M, men; RV, right ventricle; W, women.
Modified with permission from: Galea *et al.*[72]

extremely rare and may respond to surgery.[43] Medical management of the fibrotic stage may include diuretics and aspirin or anticoagulation to prevent intracardiac thrombosis. Anticoagulation can promote the re-absorption of thrombosis even in non-acute phases of the disease.[43] The fibrotic stage may occasionally require surgical therapy, which may include resection of endocardial scar as well as subchordal repair and/or valve repair or replacement.[43] Surgical resection of subendocardial fibrosis is rarely curative, even in centres of expertise. and cardiac transplantation is an option in advanced cases.

Storage disorders

This group is composed of different genetic disorders characterized by an intracellular accumulation of different substances. Iron overload cardiomyopathy is also characterized by interstitial inflammation contributing to myocardial damage. Storage disorders affect a wide spectrum of ages, including children or young adults.

Anderson–Fabry disease is the most common storage disorder and an occasional cause of RCM. It is an X-linked recessive disorder due to reduced or absent activity of α-galactosidase A (*GLA*) caused by mutations in the *GLA* gene, which results in progressive accumulation of globotriaosylceramide within tissues. Two main disease subtypes emerge: the classic multisystemic disease and the later-onset, usually associated with isolated cardiac involvement. Early cardiac involvement in males typically includes HF, arrhythmias (bradycardia, chronotropic incompetence, various degrees of atrioventricular block, AF, and ventricular arrhythmias) and mitral regurgitation, together with increased LV mass, and myocardial fibrosis. The later-onset phenotype displays similar heart manifestations developing at older ages and may be first diagnosed in patients with increased LV mass or HCM.[44] Heterozygous females can develop increased LV mass progressing to HCM and HF, usually at an older age when compared with male patients carrying the same mutation. Their disease severity may depend on the X chromosome inactivation pattern. The classical phenotype can be identified by recognizing the characteristic findings of episodic pain in the extremities, absent or decreased sweating, typical skin lesions, gastrointestinal abnormalities, and corneal dystrophy in childhood or adolescence.[45] The disease progresses to renal, cardiac and/or cerebrovascular disease in adulthood. In later-onset phenotype males, the diagnosis is often missed, and may be made in adulthood when cardiac and/or kidney involvement becomes manifest.[44] The diagnosis in males is confirmed by demonstrating the enzyme deficiency and by identifying the specific *GLA* gene mutation. Female heterozygotes can have α-*GLA* A enzymatic activity markedly decreased to values in the normal range. Therefore, heterozygous females are only accurately diagnosed by demonstrating the specific α-*GLA* gene mutation. Pathogenic mutations are associated with elevated Lyso-Gb3 a Fabry disease specific biomarker. Available treatments include enzyme replacement therapies (ERTs) (agalsidase alfa and agalsidase beta) and migalastat, which in patients with amenable mutations binds the catalytic domain of α-*GLA* A promoting its proper folding and trafficking to the lysosome.[46–48] These therapies have improved patient outcomes largely due to their renal effects. Although the cardiac positive effects are less clear, ERT may reduce the rate of cardiovascular events,[49] reduce[46,50] or stabilize LV mass, and blunt the reduction in native T1, an early CMR marker of disease.[51] New therapies for Fabry disease include second-generation ERTs, substrate reduction therapies,[52] and gene and mRNA therapies.[53]

Danon disease is a rare disorder with an X-linked dominant inheritance pattern due to mutations in the *LAMP2* gene, affecting lysosomal

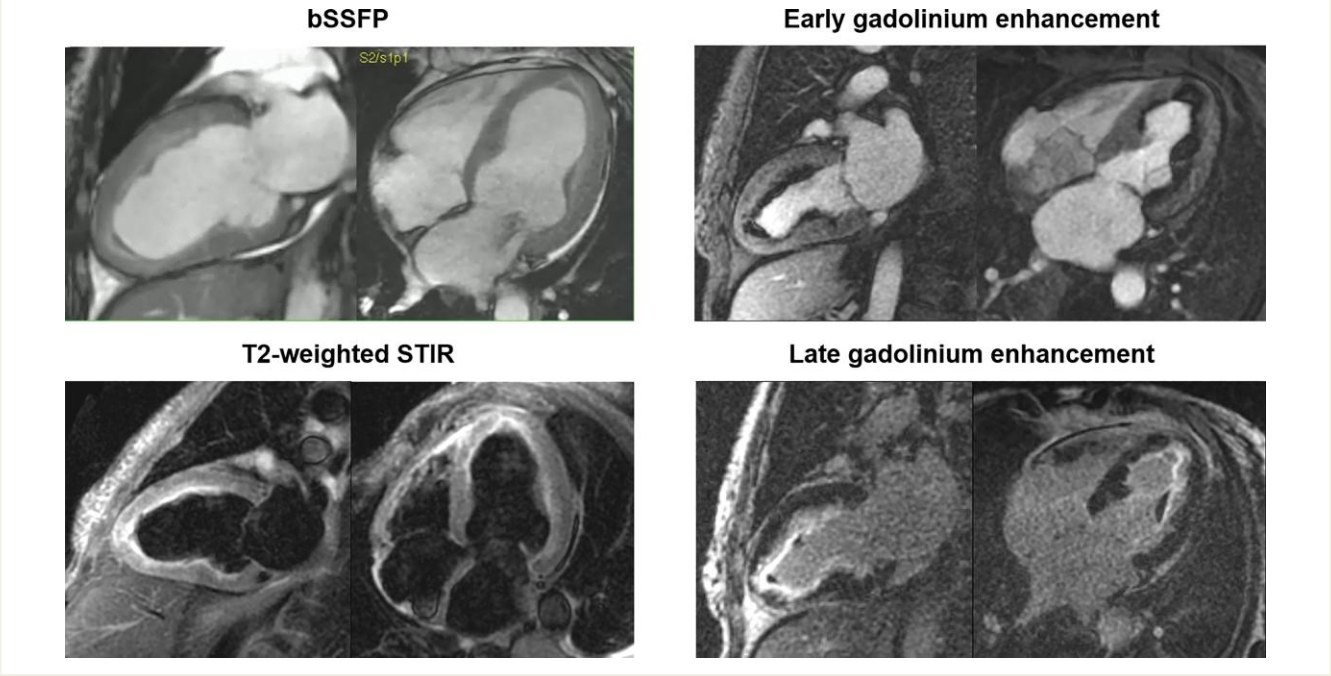

Figure 7 Cardiovascular magnetic resonance findings in a patient with early stage endomyocardial fibrosis. In a 50-year-old woman, the cardiovascular magnetic resonance examination showed evidence of active inflammation of the subendocardium (as demonstrated by myocardial oedema on T2-weighted images), and multiple intraventricular thrombi (dark images on early enhancement images).

degradation of glycogen.[54] The key features in males are cardiomyopathy, skeletal myopathy, and intellectual disability; death occurs in the second to third decade of life. Females are also affected, although usually more mildly, and the onset is often delayed until adulthood.[55,56] Different cardiac arrhythmias have been reported, including ventricular pre-excitation and AF.[57] The diagnosis is suggested by clinical history and possibly by the finding of glycogen deposits in a skeletal muscle biopsy. A non-diagnostic muscle biopsy does not exclude the diagnosis. *LAMP2* gene testing is the gold standard for diagnosis. In a Phase I trial, a single intravenous dose of RP-A501 gene therapy was generally well tolerated and led to cardiac *LAMP2B* gene expression with preliminary evidence of cardiac and extra-cardiac benefits.[58]

In iron overload cardiomyopathy, non-transferritin-bound iron promotes oxidative stress and an increase in intracellular calcium, leading to diastolic dysfunction.[59] Iron overload cardiomyopathy manifests in early stages as RCM.[60] Hereditary haemochromatosis is an autosomal recessive disorder due to mutations of genes involved in iron metabolism, causing increased iron absorption.[61] Secondary iron overload occurs primarily in patients receiving frequent transfusions because of hereditary anaemias.[61,62] In transfusion-dependent patients with acquired haematological conditions, iron chelation therapy is generally initiated after 10–20 transfusions to prevent myocardial iron accumulation.[63] Chelation therapy improves systolic and diastolic LV function and reduces mortality.[64,65] A small minority of patients now progress to a dilated phenotype and overt symptomatic HF.[42]

Desminopathies are genetic disorders characterized by the cardiac accumulation of desmin, a 53 kDa intermediate filament protein that stabilizes the sarcomere. Pathogenic *DES* mutations induce the formation of cellular aggregates, disrupting cardiomyocyte architecture and function. The transmission may be either autosomal dominant or autosomal recessive. Restrictive cardiomyopathy is one of the possible cardiac phenotypes and may be associated with advanced atrioventricular block.[66] No specific treatment is available.

Diagnostic work-up: bridging the gap between the identification of restrictive cardiomyopathy and a specific aetiology

The starting point of the diagnostic work-up for RCM is the identification of a restrictive haemodynamic profile and its persistence over time (for example, over a 6-month period).[67] Afterwards, a characterization of the echocardiographic phenotype and a 'red flag-based' approach may lead to the aetiological diagnosis[68] (*Figure 5*). This approach does not include only cardiological exams, as cardiomyopathies represent a challenging interface between cardiology and many other medical specialities. Furthermore, each step of the diagnostic work-up is valuable and can orient subsequent examinations.

The electrocardiogram (ECG) is a highly informative test providing diagnostic clues and information about the nature of the cardiomyopathy process. While infiltrative cardiomyopathies are characterized by reduced QRS complex voltages due to interstitial space expansion, storage cardiomyopathies are present with normal or increased QRS complex voltages. The discrepancy between the degree of ventricular wall thickness and QRS complex voltages on surface ECG might aid in differentiating HCM or other storage diseases from CA.

Transthoracic echocardiography is a first-line examination and may orient toward a specific diagnosis (*Figure 6*). The following step is a search for red flags of specific conditions (*Table 2*) to further inform the diagnostic work-up and allow rational use of EMB and genetic testing.

Whenever feasible, CMR should be part of the diagnostic work-up of patients with suspected RCM. Cardiovascular magnetic resonance

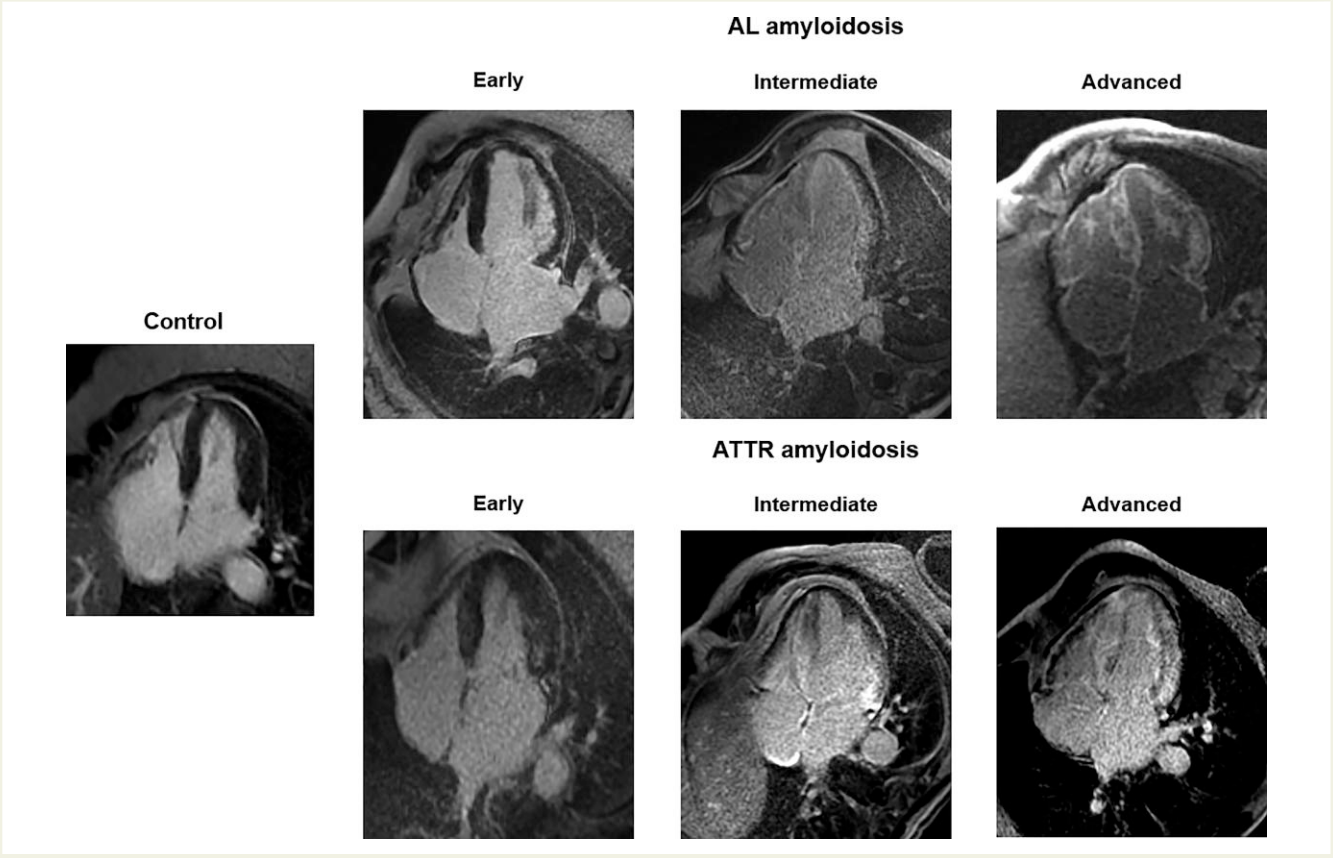

Figure 8 Patterns of late gadolinium enhancement at cardiovascular magnetic resonance across different stages of cardiac amyloidosis. Four-chamber late gadolinium enhancement images acquired 10–15 min after gadolinium administration (with an inversion time set to null the normal 'healthy' myocardium) in a healthy subject (*left*) and in patients with different stages of amyloid light-chain (*above*) or transthyretin (ATTR; *below*) cardiac amyloidosis. The circumferential subendocardial late gadolinium enhancement pattern is particularly evident in the patient with intermediate-stage amyloid light-chain amyloidosis, and the diffuse transmural pattern in patients with advanced amyloid light-chain or ATTR amyloidosis.

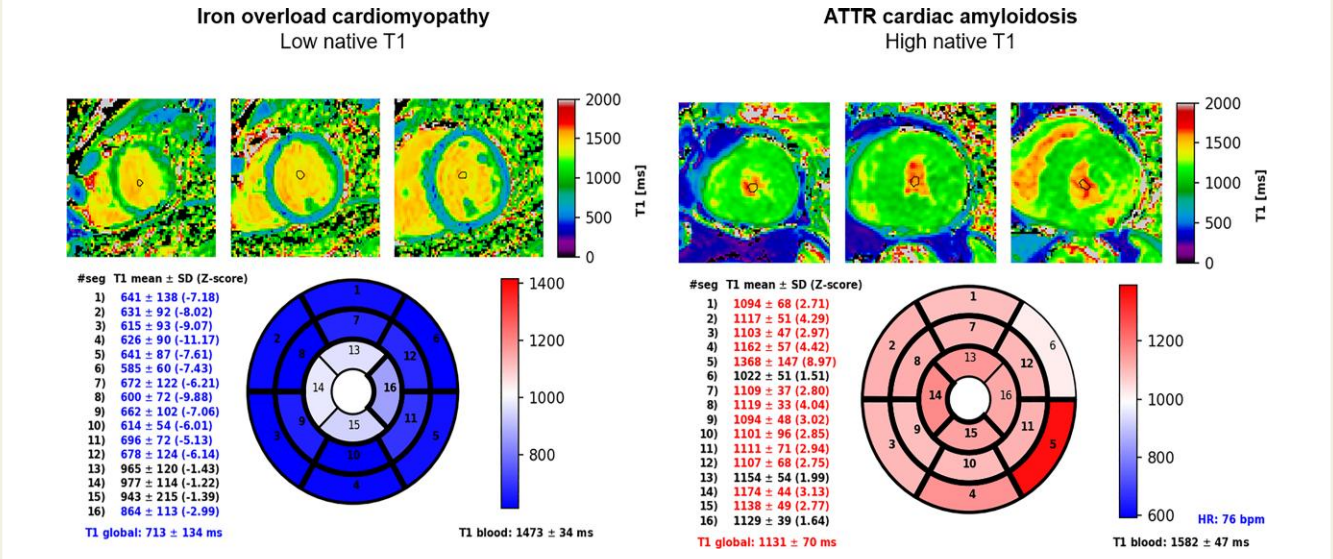

Figure 9 Mapping analyses by cardiovascular magnetic resonance. *Left panel:* low native T1 values due to iron accumulation; global myocardial T2* values were very low too (4 ms, r.v. >20 ms) *Right panel:* high native T1 values due to amyloid accumulation. Segmental T1 values are listed (±SD); *Z*-score values from a reference population are indicated in brackets.

represents the gold standard non-invasive technique to quantify biventricular volumes, mass, and EF, with cine steady-state free-precession sequences. Furthermore, CMR allows to characterize myocardial tissue properties: myocardial oedema is typically detected by T2-weighted imaging, intraventricular thrombosis with early gadolinium enhancement, and myocardial interstitial expansion with late gadolinium enhancement (LGE, usually due to fibrosis or amyloid extracellular deposition, sometimes also to myocyte necrosis or extracellular oedema). Native (i.e. pre-contrast) T1- and T2-mapping sequences provide a quantitative assessment of myocardial tissue changes; after gadolinium injection, myocardial perfusion mapping and extracellular volume (ECV) mapping provide a quantitative assessment of myocardial perfusion and of the extracellular space, respectively.[69–71] Some CMR red flags are listed in *Table 3*. As some examples, we can cite the evidence of subendocardial involvement in endomyocardial fibrosis or related disorders (*Figure 7*), and the circumferential subendocardial LGE pattern of LGE as rather characteristic of early and intermediate stages of CA, while the LGE pattern may become transmural in advanced stages (*Figure 8*). When iron overload cardiomyopathy is suspected, native T1 and T2* mapping is crucially important to detect and quantify iron accumulation as well as monitor the response to treatment. Similarly, in patients with overt cardiac hypertrophy, a low native T1 is characteristic of Fabry disease, while an increased native T1 and ECV are characteristic of CA (*Figure 9*).

Some disorders are related to specific mutations that can be detected through genetic analysis. With the use of available imaging technologies and genetics, the need for tissue biopsy has been limited to a minority of cases. Nonetheless, myocardial histology may be needed to make a definite diagnosis because of the variability of the myocardial substrate, the rarity of many disorders, and the challenging interpretation of variants with unknown significance (as in Anderson–Fabry disease and primary haemochromatosis). Defining the specific aetiology is important to decide the management strategy of the patient and his/her family. Endomyocardial biopsy is indicated whenever a clear diagnosis cannot be reached based on clinical, imaging, and genetic findings. The role of EMB in the diagnostic work-up of CA has been better defined.[26] When CA is suspected, EMB can be avoided when there is an intense myocardial uptake of bone tracers on scintigraphy, and no monoclonal protein is found.[26] Furthermore, AL-CA can be diagnosed without an EMB when an extracardiac biopsy is positive for AL amyloid and echocardiographic or CMR criteria for cardiac involvement are met.[26]

Conclusions

The current classification of cardiomyopathies has deeply transformed our approach to the diagnosis of disease and has improved our understanding of this heterogeneous field. The attempt to dissect the heterogeneous variety of cardiomyopathies with a clinically relevant and feasible approach represents one of the hardest challenges of the contemporary era. Based on these premises, we carried out a critical revision of the current definition of RCM, starting from the ESC recommended approach, to shed light upon the grey zone of this cardiomyopathy model, following major advances in knowledge achieved over recent years.

The essence of RCM is the coexistence of persistent restrictive physiology, commonly with atrial dilatation, and nondilated ventricles, regardless of ventricular wall thickness and systolic function. A restrictive filling pattern on echocardiography at a single time is not sufficient to diagnose RCM, as this finding might result from transient haemodynamic alterations. Unlike the ventricular thickness and dilatation that define HCM and DCM, respectively, the restrictive filling pattern can be dynamic and reversible over short time intervals (i.e. severe congestion relieved with diuretics). Therefore, it would be reasonable to consider 'persistent' restrictive pathophysiology as the presence of a restrictive filling pattern on at least two repeated Doppler echocardiograms: (i) at clinical presentation and (ii) after an appropriate period (e.g. at least six months). In the time window between clinical presentation and confirmation of a persistent restrictive pathophysiology, patients might be defined as having a 'possible RCM', and undergo a search for the disease substrate. In general, we believe that a useful and clinically feasible classification based on cardiac phenotype on echocardiogram should simply provide a 'nosographic box' for each patient rather than a presumptive diagnosis. In this perspective, the identification of the predominant phenotype at presentation should be considered to classify patients in one of the following 'boxes': dilated phenotype, hypertrophic phenotype, or restrictive phenotype. This approach would provide a clinical guide but would also maintain a broad and open horizon of the possible final diagnosis. A clear example is provided by 'restrictive pathophysiology' which can be the very essence of cardiomyopathy (RCM) or an accompanying feature (HCM or DCM with restrictive pathophysiology). Patients with mild increases in ventricular wall thickness and restrictive filling pattern should be considered as possible RCM rather than HCM at first clinical evaluation, as the predominant feature is diastolic impairment. On the other hand, patients with severe increase in ventricular wall thickness and restrictive filling pattern should be considered as HCM with restrictive pathophysiology as 'cardiac hypertrophy' is the predominant feature. This approach might be reasonable and provide an initial nosographic box to classify patients without the claim that a definitive diagnosis can be made at the first clinical evaluation (*Figure 5*).

The histological substrate of RCM is highly variable, even when adopting the new definition of RCM, but four subgroups can be identified: infiltrative diseases, interstitial fibrosis/intrinsic myocyte dysfunction, endomyocardial diseases, and storage disorders. Including the histological substrate may be useful to categorize the disorders classified as RCM rather than from a diagnostic perspective, as the EMB is performed near the end of each diagnostic work-up and is not always required. The diagnostic approach proposed in *Figure 5* should be applied to a patient with RCM, defined as above. The final diagnosis will be the specific disorder (with the features of RCM), or 'primary RCM' when other disorders are excluded.

The main messages for clinicians are recapitulated in Box 1.

Box 1 Proposed new approach to RCM: clinical implications

- RCM should be suspected in patients with a restrictive pathophysiology and no ventricular dilatation.
- The restrictive pathophysiology should be confirmed in repeated evaluations.
- When RCM is identified, the echocardiographic patterns (normal or increased LV thickness or evidence of endomyocardial involvement) may orient toward a specific diagnosis.
- Red flags of specific conditions should be searched among clinical, ECG, imaging findings.

ECG, electrocardiogram; LV, left ventricular; RCM, restrictive cardiomyopathy.

Conflict of interest: None declared.

Data availability

Not applicable (no original data are presented).

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