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REVIEW

Role of cardiovascular magnetic resonance in the clinical evaluation of left ventricular hypertrophy: a 360° panorama

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Abstract

Left ventricular hypertrophy (LVH) is a frequent imaging finding in the general population. In order to identify the precise etiology, a comprehensive diagnostic approach should be adopted, including the prevalence of each entity that may cause LVH, family history, clinical, electrocardiographic and imaging findings. By providing a detailed evaluation of the myocardium, cardiovascular magnetic resonance (CMR) has assumed a central role in the differential diagnosis of left ventricular hypertrophy, with the technique of parametric imaging allowing more refined tissue characterization. This article aims to establish a parallel between pathophysiological features and imaging findings through the broad spectrum of LVH entities, emphasizing the role of CMR in the differential diagnosis.

Keywords Left ventricular hypertrophy · Cardiovascular magnetic resonance · Differential diagnosis

Left ventricular hypertrophy (LVH) is a frequent imaging finding in the general population, as detected by imaging [1, 2]. Unless it is a physiological adaptation, LVH is clinically relevant since it constitutes a marker of adverse prognosis including major cardiovascular events [3, 4]. However, LVH is not a diagnosis per se but a phenotype resulting from several myocardial processes. An extensive evaluation of the family history, extra-cardiac abnormalities, the electrocardiographic pattern and echocardiographic findings aid in determining the etiology.

Left ventricular (LV) size is influenced by gender, age, ethnicity, body mass index and physical activity—although its relative geometry is relatively independent of body size [5, 6]. When LV mass and/or relative wall thickness (the ratio of twice the posterior wall thickness to LV diastolic diameter) are increased, a remodeling process has occurred resulting in LVH. LVH may result in an increase of total LV mass, or may manifest as a more focal phenomenon with increase of LV wall thickness in a few segments.

When LVH is detected, the prevalence of each etiology should be considered (Fig. 1). Physiologic increase in cardiac mass and wall thickness may occur in highly trained individuals—although this is not the rule, especially in women—and only a mild wall thickness increase (≤ 12 mm) is observed in the majority of the athletes [7, 8]. Physiologic hypertrophy reflects cardiac adaptation to exercise, consisting in a proportional growth of muscular and non-muscular compartments, and a balanced thickness-to-cavity ratio.

Coronary microvascular dysfunction (CMD) resulting from microvascular remodelling and extravascular compression often coexists with pathologic LVH [9, 10].

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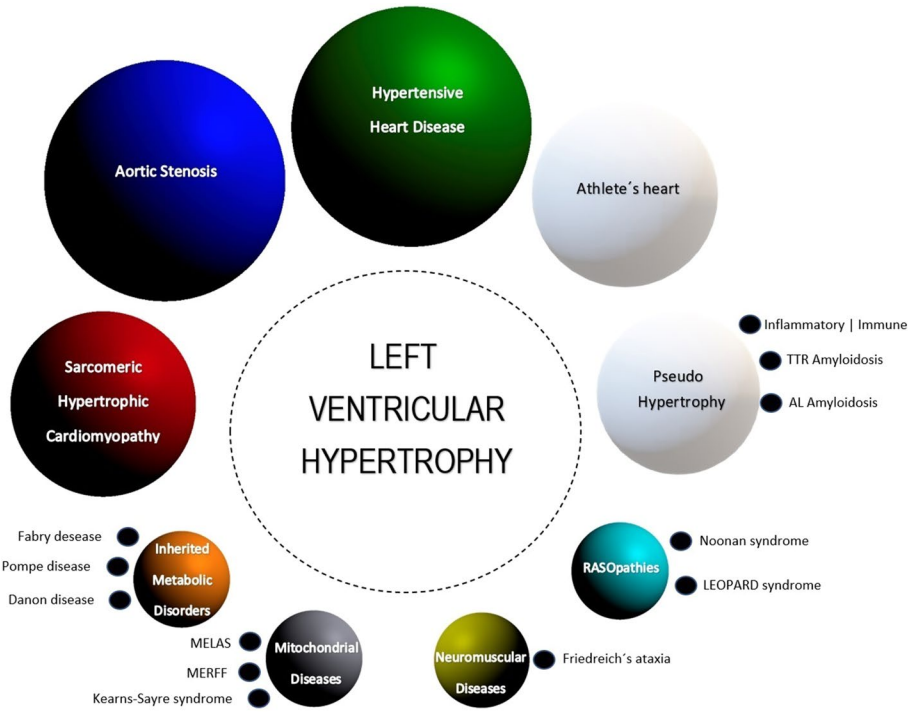

Fig. 1 Left ventricular hypertrophy—360° panorama. The importance of bearing in mind the prevalence of each etiology in the differential diagnostic process

Pressure overload is the most frequent cause of pathologic LVH, due to the high prevalence of arterial hypertension (HTN) and aortic stenosis (AS) in the general population. In the absence of abnormal loading conditions, sarcomeric hypertrophic cardiomyopathy (HCM) is the most likely diagnosis, particularly in young patients.

Pathologic LVH may be the hallmark of inherited metabolic disorders, such as Fabry or Danon disease [11, 12]. Aptly termed *storage* diseases, the accumulation of metabolic products accounts only for a small percentage of the increase in cardiac mass, which is largely due to true myocyte hypertrophy, triggered by unknown mechanisms. Conversely, "pseudo"-hypertrophy is typical of infiltrative diseases characterized by extra-cellular deposits, as in cardiac amyloidosis, or diffuse myocardial edema caused by acute in inflammatory diseases. In older patients, more than one disease may coexist e.g., AS and HTN, AS and amyloid, AS and HCM, and amyloid and HCM.

Different pathophysiological mechanisms lead to distinct imaging findings, through the broad spectrum of LVH. This review aims to summarize how CMR may depict the pathological features beyond LV morphology, by performing a parallelism between pathophysiological features and imaging findings for each entity, providing a 360° panorama of LVH beyond plain sight.

The role of cardiovascular magnetic resonance

CMR has emerged as the gold standard imaging technique to characterize abnormalities of myocardial structure and function, able to differentiate features of LVH in various contexts. As result of its spatial resolution it allows a detailed characterization of LVH severity and distribution and accurate measurement of mass, volumes and function, more reliably compared to echocardiography [13, 14]. Furthermore, the most important additional value of CMR comparing to echocardiography is likely the capacity for tissue characterization.

By using CMR to evaluate LV mass, no uniformly accepted convention has been used for analysing papillary muscle mass, and current recommendations indicate that these structures should be consistently included in the LV volume or in the LV mass [15]. Reflecting the discrepancy in the values for LV mass through the different studies, the normal range values slightly vary between consensus documents [15, 16]. In the European Association of Cardiovascular Imaging expert consensus (2019) the normal range for LV mass is 49–85 g/m^2 for adult males and 41–81 g/m^2 for adult females, with papillary muscle mass included in the LV mass [16].

Furthermore, CMR details the severity of LVH, its morphology, allows tissue characterization, detection of inflammation and ischemia. Parametric mapping techniques measure the T1 and T2 relaxation times of each voxel in the

myocardium, building a visual map that allows quantification (Table 1; Fig. 2).

(a) Native T1 mapping measures both intracellular and extracellular components. In the presence of LVH, T1 may reflect cellular hypertrophy, extracellular fibrosis and/or edema. Its value increases with interstitial fibrosis and edema, and decreases with intracellular accumulation of iron or lipids [17, 18].
(b) Myocardial extracellular volume (ECV) can be calculated using pre- and post-contrast T1 maps. ECV is used as a surrogate measure specifically aimed at the extracellular space [17, 18], with correlation with interstitial fibrosis by endomyocardial biopsy [19]. Increased ECV may also occur from diffuse protein deposition or edema [20].
(c) T2 values are useful to detect interstitial edema [17, 18]. Thus, in the presence of increased ECV, T2 mapping allows the distinction between interstitial fibrosis and concomitant edema.
(d) Late gadolinium enhancement (LGE) imaging identifies replacement fibrosis in a variety of cardiac diseases, but is less sensitive to detect diffuse interstitial collagen deposition [21, 22].

The incorporation of mapping data and LGE patterns are rapidly becoming a key tool in clinical practice in the evaluation of certain conditions. Despite the additional role of parametric mapping in the detection of interstitial fibrosis, its importance in differential diagnosis is reserved for entities with extreme values as cardiac amyloid or Fabry disease, as there is a significant overlap between different entities and even with normal individuals. LGE keeps its role mainly as a marker of pathological process and well stablished prognostic value.

Despite the unquestionable importance of CMR in assessing cardiac morphology, function and tissue characterization, images per se should never lead to a diagnosis disconnected from patients' clinical profiles, as a significant overlap in imaging findings may be found between some entities, and more than one pathological process may be present simultaneously (for example hypertension and HCM; aortic stenosis and amyloidosis). In the evaluation of LVH, a family history and extensive clinical evaluation, including extra cardiac features, should complement findings on electrocardiography and echocardiography as the first step. Subsequently, CMR with detailed tissue characterization, provides additional details to increase the diagnostic objectivity (Fig. 3).

Physiologic hypertrophy

Athlete's heart

Regular exercise leads to cardiac physiological adaption, which encompasses electrical, structural and functional changes. In a subset of highly trained individuals, it may cause the "Athlete's heart", a balanced increase in left and right cardiac cavity size and LV wall thickness. Compared to those of pathologic LVH, such changes are usually modest and usually fall within accepted normal limits [8, 23]. The prevalence and extent of these changes reflects a polygenic background as well as gender and ethnicity. Notably, LV wall thickness > 12 mm is only seen in 2% of white athletes (and virtually never in women), but up to 18% in black athletes [8]. Even in the presence of pronounced increase in LV wall thickness in endurance athletes, it is balanced with associated increase in LV cavity size, and conserved indices of diastolic function. Increased LV

Table 1 Mapping findings in the different etiologies of left ventricular hypertrophy

Entity	Native T1	Extracellular volume	T2
Athlete's heart	↔↓	↔↓	↔
Hypertensive cardiomyopathy	↑	↑	↔
Aortic stenosis	↑	↑	↔
Hypertrophic cardiomyopathy	↑↑	↑↑	↔↑
Fabry disease	↓↓↓	↔	↔↑
TTR amyloidosis	↑↑↑	↑↑↑↑	↑
AL amyloidosis	↑↑↑↑	↑↑↑	↑↑
Myocardial inflammation	↑↑	↑↑	↑↑

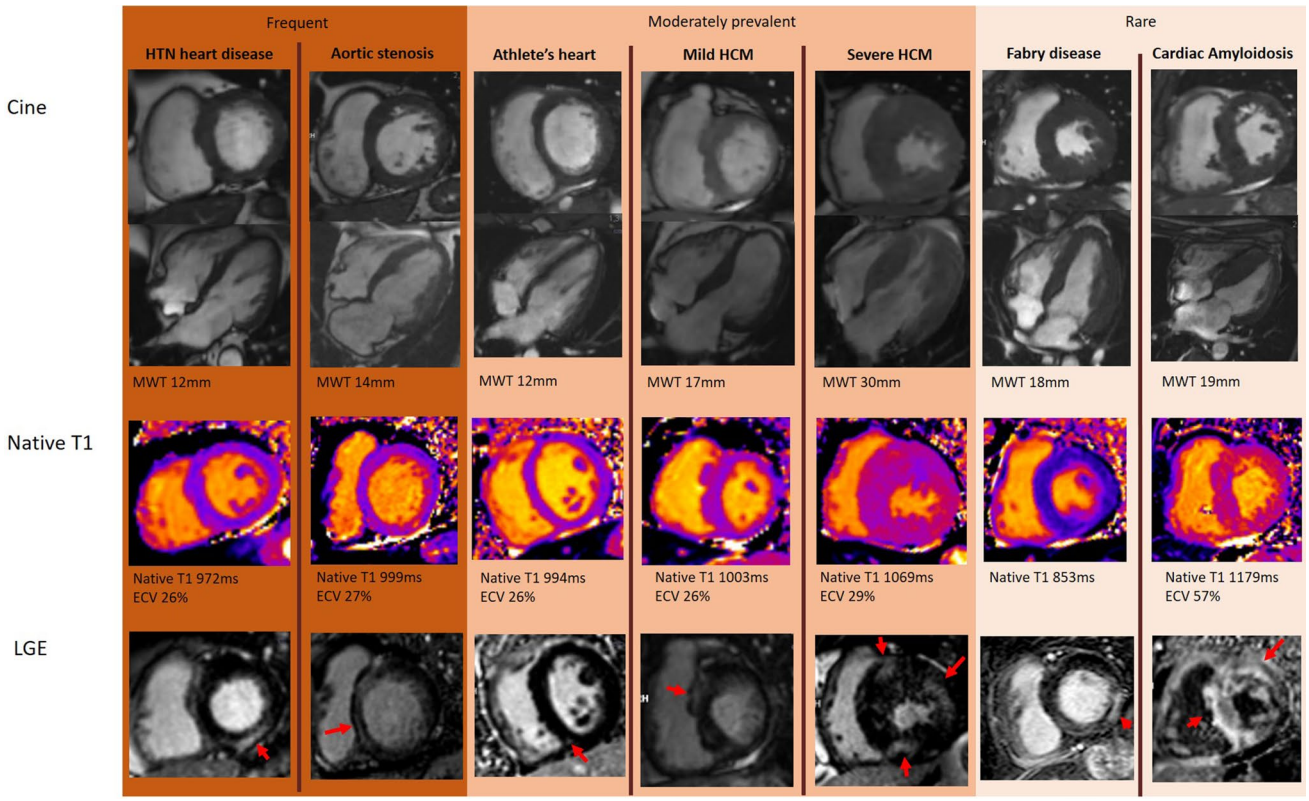

Fig. 2 Imaging findings through the spectrum of left ventricular hypertrophy (LVH). Two frequent causes of LVH: hypertensive (HTN) heart disease and aortic stenosis showing mild and asymmetric LVH with maximal wall thickness (MWT) of 12-14 mm, normal native T1 and extracellular volume (ECV), intramural late gadolinium enhancement (LGE) (red arrows). Athlete´s heart with balanced left and right cardiac cavity sizes, mild LVH, normal native T1 and ECV and LGE in the right ventricular insertion point. Mild and severe hypertrophic cardiomyopathy (HCM) showing the association between the severity of LVH and increased values of native T1 and ECV and more extensive LGE. Fabry disease denoting concentric LVH with prominent hypertrophy of papillary muscle, low values of native T1 representing the sphingolipid accumulation and LGE in the inferolateral wall. Cardiac amyloidosis showing asymmetric LVH, markedly increased native T1 and ECV and diffuse LGE with characteristic gadolinium kinetic

wall thickness is the result of myocyte hypertrophy with side-by-side addition of sarcomeres, rather than increased extracellular matrix [24]. CMR detects this as a relative decrease in extracellular compartment, with normal or slightly decreased ECV [25, 26]. Adequate detraining usually reverses physiologic LVH related to exercise [27]. Additionally, anabolic–androgenic steroids misused by some athletes and body builders further drive cardiac muscle growth contributing for LVH, however these changes in LV wall thickness may not recover with discontinuation of the drug [28, 29].

LGE detected at the RV insertion points into the septum may represent microinjuries due to RV pressure/volume overload during exercise [25, 30]. Subepicardial or midmyocardial LGE in the inferolateral wall or interventricular septum have been reported in athletes and may represent previous myocarditis or an undiagnosed cardiomyopathy in its preclinical stages**,** rather than part of the physiological remodeling of the athlete's heart.

Pathologic hypertrophy

Pressure overload

Hypertensive heart disease

Arterial hypertension is the most common cause of LVH worldwide. To counter the increased afterload and LV wall stress, hypertensive hearts develop structural remodeling resulting in increased cellular size (hypertrophy) and addition of myofibrills in-parallel and in-series (hyperplasia). This cellular adaption leads to concentric LV wall thickening [31–33]. Fibroblast proliferation and increased collagen formation lead to diffuse fibrosis of the interstitial and perivascular space [34, 35]. Extracellular matrix expansion and accumulation of interstitial collagen fibers can be detected by CMR. In hypertensive patients with LVH, which develops over time, native T1 mapping and ECV are elevated, and native T1 and ECV are higher in hypertensive LVH subjects

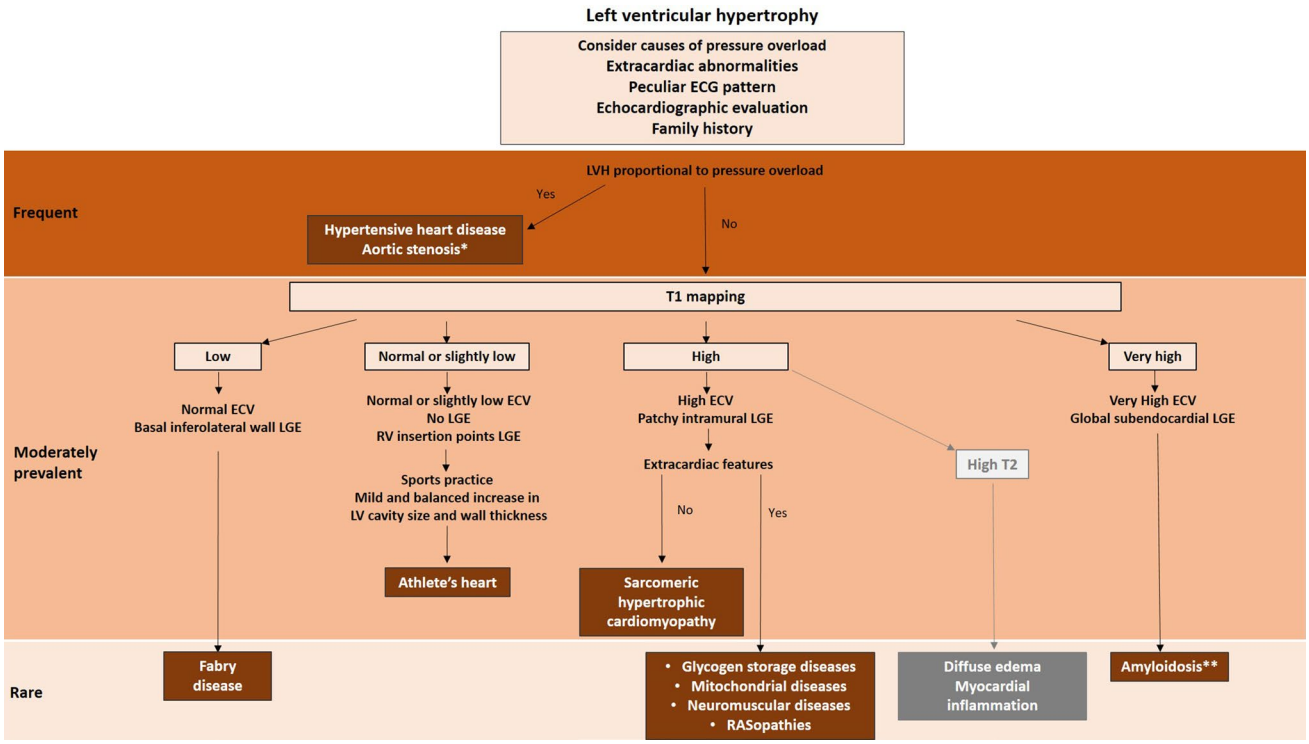

Fig. 3 Integration of CMR in the differential diagnosis of left ventricular hypertrophy. *Tissue characterization by CMR may be useful to exclude concomitant entities, more commonly cardiac amyloidosis. **Early involvement by amyloid may present only slight elevation of native T1 and ECV, that may overlap with other etiologies, such as hypertrophic cardiomyopathy with significant fibrosis. *ECV* extracellular volume, *LGE* late gadolinium enhancement, *LVH* left ventricular hypertrophy, *RV* right ventricular

comparing to hypertensive non-LVH [33]. ECV can identify the abnormalities in extracellular matrix before the appearance of LGE [33, 36, 37].

Focal fibrosis may also be found. LV remodeling, including enlarged LV mass, and increased LV wall stress have been linked to midwall fibrosis on CMR studies [38], and may potentially constitute contributors for the LGE pattern found in hypertensive heart disease. LGE is usually detected in a patchy midwall pattern within the LV, and may also be evident at the RV insertion point [39].

Secondary hypertension

While LVH in essential HTN is generally mild and concentric, patients with secondary forms of hypertension more often exhibit severe and diverse patterns of hypertrophy and may develop phenotypes resembling cardiomyopathies [40].

In renovascular hypertension, sympathetic nerve fibres stimulate cardiomyocyte alpha-adrenergic receptors leading to LVH, while renal denervation therapy has the potential of reducing LV mass [41]. Furthermore LVH is a result of the effects of molecules such as angiotensin II, aldosterone, or catecholamines, that stimulate muscle cell growth independently of blood pressure, and may cause myocardial cell hypertrophy and/or hyperplasia and promotes collagen deposition and interstitial myocardial fibrosis [42].

Patients with primary aldosteronism have greater degrees of LVH and concentric remodeling when compared to those with essential HTN [43] and often exhibit a non-ischemic LGE pattern [44, 45].

Among patients with Cushing syndrome, the prevalence and severity of LVH and fibrosis are increased compared with essential HTN. Structural abnormalities, including increased LV mass, are only partially explained by the rise in blood pressure, while the most important role is attributed to the excess cortisol secretion. Other Cushing's syndrome-related cardiovascular risk factors such as visceral obesity, glucose intolerance, and dyslipidemia may also contribute to LVH [46]. These patients show increased myocardial fibrosis [47], and perivascular inflammation [48], which leads to increased native T1 values [49].

Pheochromocytomas are neuroendocrine catecholamine-secreting tumors, that frequently lead to hypertensive crisis and deleterious cardiac effects, namely cardiac hypertrophy, myocarditis and myocardial fibrosis. Consequently, increased LV mass, systolic dysfunction, increased native T1 and LGE may be found on imaging [50]. After treatment, recovery of LV ejection fraction

and regression in LVH is noted, but elevated T1 and LGE persist [50].

Thyroid hormones directly promote LVH independent of associated HTN, and increased LV mass has been described even in subclinical hyperthyroidism [51, 52].

In acromegalic cardiomyopathy, circulating growth hormone (GH) and insulin-like growth factor-1 activate myocyte growth resulting in biventricular hypertrophy [53]. GH promotes collagen synthesis and deposition [54], which are demonstrated by midwall LGE on CMR [55], present in a minority of patients [55, 56]. Myocardial edema is also an important histologic feature, reversible after treatment [57, 58].

LVH is a common finding in patients with obstructive sleep apnea, along with RV hypertrophy and LA enlargement. Biventricular hypertrophy is the result of increased preload and afterload, generated by the exacerbated negative intrathoracic pressures during inspiratory efforts, increased venous return and stimulation of sympathetic system activity [59]. The concomitant hypertension, diabetes and obesity in these patients may further contribute for LVH.

In children and young adults, coarctation of the aorta is an important cause of hypertension, representing a classic model of chronic pressure overload, leading to LVH [60] which seems to be less often associated with myocardial fibrosis compared to other genetic causes of LVH [61]. Other congenital models of pressure overload may also lead to LVH. Subvalvular aortic stenosis, presenting as a thin membrane just below the aortic valve, thick fibromuscular ridge, or long and narrow fibromuscular channel along the LV outflow tract [62]. On the other hand, supravalvular aortic stenosis is a systemic elastin arteriopathy that includes congenital narrowing of the lumen of the aorta. This condition may be present in non-syndromic or syndromic conditions such as Williams–Beuren syndrome [63].

Aortic valve stenosis

In AS, LV wall thickening is typically concentric, although asymmetric patterns preferentially involving the interventricular septum may occur. Histological abnormalities include myocyte hypertrophy and interstitial fibrosis. In AS, capillary density and coronary flow reserve are reduced. Structural changes in intramural coronary vessels are less pronounced in aortic stenosis compared to hypertensive heart disease, and CMD is primarily a result of extravascular mechanisms, secondary to LVH and diastolic dysfunction [9, 64, 65].

Electron microscopy demonstrates areas of progressive degenerative injury of cardiomyocytes, culminating in cellular atrophy, myocyte death and replacement fibrosis [66]. Men with AS have more prominent LVH than women and develop a less favorable, maladaptive ventricular phenotype with focal fibrosis and extracellular expansion, resulting in higher indexed extracellular matrix and ECV [67]. This gender difference may be due to greater activation of profibrotic and inflammatory pathways in men, and differential expression of androgen and estrogen receptors [67]. CMR studies have shown that the extent of diffuse myocardial fibrosis is a strong determinant of functional status and mortality [68, 69]. Recent data have shown a correlation between ECV and LV mass, left atrial volume, New York Heart Association functional class, LGE and lower LV ejection fraction. ECV is an independent predictor of cardiovascular and all-cause mortality [70]. LGE is consistently more prevalent in males [39, 71], exhibiting a midwall pattern which is an independent predictor of mortality in patients with moderate and severe AS [72, 73]. After aortic valve replacement, cellular hypertrophy and diffuse myocardial fibrosis may be reversible, as demonstrated in myocardial biopsies [74], and more recently by CMR studying ECV [75]. However, cardiomyocyte loss is irreversible and replacement fibrosis depicted by LGE does not regress [75].

AS may occasionally be associated with transthyretin cardiac amyloidosis [76]. Evaluation of AS patients should include the assessment of typical cardiac amyloidosis findings to rule-out the coexistence of the two disorders**.** A disproportionate level of LVH, for example in a patient with severe AS but no concomitant hypertension or even moderate AS, should raise the possibility of amyloidosis and a CMR study may be worthwhile [77]. LGE, native T1 and ECV values become progressively abnormal with the increase of amyloid burden. Patients with concomitant cardiac amyloidosis and AS have higher native T1 and ECV values [78]. Extremely high values of T1 and ECV (particularly T1 higher than 1164 ms and ECV higher than 37%) in a patient with AS should lead one to consider coexistent amyloid [79], as it does a circumferential and extensive LGE which starts from the subendocardium and predominates at the basal segments [77]. Persistent LVH with minimal regression post-treatment is another clinical clue, if a CMR was not done prior to valve replacement.

Genetic cardiomyopathies causing LVH

Hypertrophic cardiomyopathy Hypertrophic cardiomyopathy (HCM) is defined by the presence of LVH, unexplained by abnormal loading conditions. The disease is inherited as an autosomal dominant trait, caused by mutations in cardiac sarcomeric genes [80, 81], although the diagnostic yield of genetic testing is 30–40% generically, being influenced by the LVH pattern and severity, age at diagnosis, or family history [82, 83]. The classic LVH pattern is asymmetric, affecting the basal and mid anteroseptal segments, although a huge number of variants have been described, including apical and concentric phenotypes (Fig. 4) [84]. This hetero-

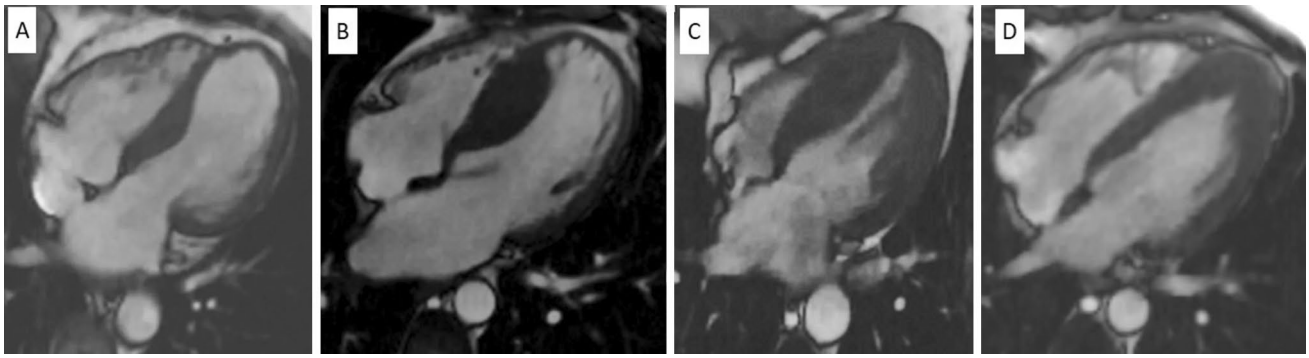

Fig. 4 Left ventricular hypertrophy patterns in hypertrophic cardiomyopathy: asymmetric septal (**A**, **B**), concentric (**C**) and apical (**D**)

geneity is also noted in the patchy distribution of cardiomyocyte disarray, since severely disarrayed myocytes may appear adjacent to normally sized and normally aligned myocytes. This unequal distribution might reflect cell to cell differences in gene expression and autocrine production [85]. HCM patients may have markedly coronary microvascular dysfunction due to severe microvascular remodelling, although other mechanisms exist, including reduced capillary density, myocyte disarray, extravascular compression due to LVH, diastolic dysfunction and LV outflow obstruction [85–87]. Coronary microvascular dysfunction in patients with HCM has been assessed by CMR, showing decreased hyperemic myocardial blood flow/vasodilator response, mainly in the endocardium, and demonstrating a link to wall thickness, tissue abnormalities, arrhythmias and functional capacity [88–91].

Two patterns of fibrosis may be found histologically in HCM—diffuse interstitial fibrosis and replacement fibrosis [22, 92]. Interstitial fibrosis results from fibroblast activity and increased number and thickness of collagen fiber component of the matrix, arranged in disorganized patterns [93]. Native T1 and ECV correlates with diffuse fibrosis, elevated even in areas without LGE [21, 94, 95], and were found to be elevated in genotype-positive patients without overt hypertrophy [94]. On the other hand, progressive myocyte loss and necrosis results in replacement fibrosis [92]. LGE in HCM patients has a typical midwall pattern localized in the hypertrophied segments. In advanced disease, LGE increases considerably and, in patients developing end-stage features, can be transmural and occupy up to 40% of the LV, with relevant prognostic consequences [21, 92, 93]. LGE extent is also associated with arrhythmic risk constituting one of the risk factors for sudden cardiac death taken into consideration for prophylactic implantable cardioverter defibrillator [80, 96].

Myocardial edema has been described in patients with HCM. T2-weighted imaging showed hyperintensity in areas which may or may not be coincident with LGE, associated with signs of advanced disease, such as higher LV mass, lower ejection fraction and greater LGE extent, and higher arrhythmic risk [97].

Diffusion tensor CMR has emerged as a potential marker of disarray, since this structural abnormality may be inferred by mapping the preferential diffusion of water along cardiac muscle fibers [98]. In HCM, this technique showed that sheetlet mobility is impaired and the diastolic orientations appear markedly abnormal, mainly in more hypertrophied segments[99]. Despite the promising role of this technique, its use is not widespread and clinical value remains unknown.

Besides evaluating the myocardium, other features are detected on CMR, include mitral leaflet and papillary muscle abnormalities, LV outflow obstruction and crypts [100].

Rare cardiomyopathies A broad spectrum of rare genetic diseases may manifest as LVH (Fig. 5). However, extracardiac abnormalities are important clinical features, providing relevant clues for the differential diagnosis. Although pathognomonic CMR findings can be found in some entities, such as Fabry disease, other diagnoses require a focus on clinical clues to clinch the diagnosis, reflecting the fact that imaging alone does not provide all the answers.

In Fabry disease, LVH has a concentric pattern in the majority of cases, although other pattern of LVH may also be found. Additionally, it is also frequent a diffuse involvement of the LV papillary muscles and the right ventricle [11, 101, 102]. Chronic accumulation of globotriaosylceramide contributes itself to LVH, and further triggers sarcomeric protein expression leading to myocyte hypertrophy [103–105]. As sphingolipid storage is mainly an intracellular phenomenon and extracellular space is spared by accumulation, native T1 values are low (as fat has low T1 mapping values), while ECV remains normal. The fall in T1 with age is steeper in men, suggesting that storage is faster in men than in women [11]. Patients receiving enzyme replacement therapy show less shortening of T1, and may also present reduction in T2 in correlation with the reduction in LV mass [106–108]. In more advance stages of the disease, with the

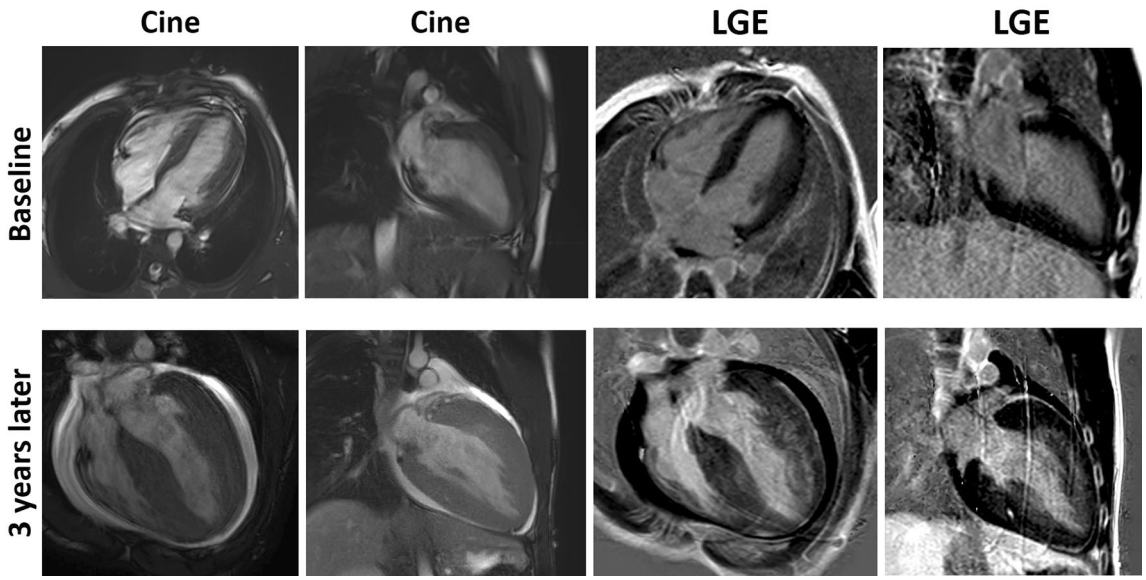

Fig. 5 A case of Danon disease with fast progression. Baseline: 11-year-old Afro-Carribean male teenager with recent diagnosis of mild concentric left ventricular hypertrophy (11 mm) CMR showed absence of late gadolinium enhancement (LGE), native T1 1039 ms, extracellular volume (ECV) 28%. Since the patient was adopted, family history was unknown. Clinically asymptomatic with an unremarkable physical examination. Normal mental and somatic growth was reported. Three years later, massive and abrupt progression of myocardial hypertrophy was noted. Left ventricular hypertrophy had asymmetric septal pattern with a maximum wall thickness of 20 mm. Moderate circumferential pericardial effusion was noted. Tissue characterization evidenced diffuse LGE, native T1 of 1110 ms and ECV 30% (native T1 normal range 970 ± 40 ms)

progression of myocyte hypertrophy and myocardial fibrosis, native T1 shows pseudo-normalization and ECV increases [11, 109, 110]. LGE is typically located in the basal inferolateral wall, probably reflecting inflammation in the initial stages accompanied by T2 elevation, and scar with the disease progression [111]. By providing a comprehensive tissue dissection, CMR has assumed a central role in diagnosis and staging of Fabry disease [105].

In Friedreich's ataxia, besides cellular hypertrophy, the deficiency of frataxin leads to mitochondrial iron accumulation in cardiomyocytes, mitochondrial damage, necrosis and myocardial fibrosis [112–117]. This process is depicted by LGE that may be found even in the absence of severe LVH [118, 119].

In RASopathies, a particular pattern of hypertrophy beyond the LV includes involvement of RV outflow tracts with dynamic obstruction and midventricular stenosis due to hypertrophied moderator band with muscle bundles [120, 121].

Mitochondrial diseases are characterized by deficiencies in the mitochondrial oxidative phosphorylation system, leading to diffuse cellular hypertrophy with swollen and often vacuolated cardiomyocytes [122, 123]. Perturbations in cellular energetic metabolism further cause cell death and replacement fibrosis [124]. Imaging shows concentric, non-obstructive LVH, potentially with evolution to LV dilation and dysfunction, and LV trabeculae may be prominent [124]. Intramural or subepicardial pattern of LGE reflects the myocardial fibrosis, and may precede LVH [125].

More details regarding these rare disorders are shown in Table 2.

"Pseudo-hypertrophy"

In some entities, increased LVH is the manifestation of interstitial space expansion rather than true cellular hypertrophy. Cardiac amyloidosis is the classical example where amyloid fibrils deposit in extracellular space causing LVH [126]. Genetically mutated or wild-type transthyretin (ATTR) and immunoglobulin-derived light chains (AL) amyloidosis are responsible for the vast majority of cardiac amyloidosis [127, 128]. The two entities have very similar morphology but differ substantially in myocardial tracer uptake with bone scintigraphy, and have different clinical profiles. While ATTR amyloidosis has a slower clinical course, behaving more like a cardiomyopathy, AL amyloidosis resembles myocarditis, due to the toxic effect of light chains within the heart. In these patients, myocardial edema associated with light chain or fibril toxicity further increases extracellular fraction [129]. CMR parametric imaging has a crucial role in the diagnosis of cardiac amyloidosis [79] by detecting very high values of native T1 and ECV reflecting the massive extracellular expansion (cut-off of 1164 ms for native

Table 2 Etiology for left ventricular hypertrophy—pathophysiological features and tissue characterization by cardiovascular magnetic resonance

Disease	Pathophysiological features				Tissue characterization		
	Extent/distribution of left ventricular hypertrophy	Fibrosis/extracellular matrix	Microcirculation	Disarray/cellular abnormalities	Late gadolinium enhancement	Parametric Mapping	Extracellular volume
Physiologic hypertrophy							
Athlete´s heart	Balanced increase in the left and right cardiac cavity sizes	Relative decrease of the extracellular compartment	Increased coronary flow capacity Improved endothelial function	Cellular hypertrophy Microinjuries in RV insertion points	Absent Mid-myocardial in the RV insertion points	Normal or decreased T1	Normal or decreased
Pressure overload							
Hypertensive heart disease	Concentric LVH	Myocardial and perivascular space fibrosis. Focal and diffuse myocardial fibrosis	Reduction of capillary density; medial hypertrophy	Cardiomyocyte hypertrophy	LV mid-wall; patchy RV insertion points; papillary muscles	Increased native T1 (overlap with normal)	Increased ECV reflects diffuse myocardial fibrosis
Secondary hypertension	LVH disproportionate to the duration of HTN	Interstitial space expansion and myocardial fibrosis	Aldosterone promotes vascular smooth cell hypertrophy/hyperplasia and endothelial dysfunction Cortisol induces perivascular inflammation	Angiotensin II, cortisol, GH and IGF-1 promote myocyte hypertrophy and/or hyperplasia Catecholamine secreted by pheochromocytoma have direct toxic effect on myocytes	Nonsubendocardial in primary aldosteronism, pheochromocytoma acromegalic cardiomyopathy LGE does not seem frequent in Cushing´s syndrome and hypothyroidism	Increased native T1 in Cushing's syndrome; Pheochromocytoma, Hypothyroidism	
Aortic stenosis	Concentric LVH, more marked in men	Diffuse myocardial fibrosis	Reduction of resistance vessels; perimyocytic fibrosis	Cardiomyocyte degeneration and apoptosis	Nonsubendocardial; diffuse, patchy; RV insertion points; papillary muscle	Increased native T1 (overlap with normal)	Increased ECV due to fibrosis
Genetic							
Sarcomeric hypertrophic cardiomyopathy	Asymmetric or widespread LVH Most patients have a significant proportion of myocardium spared from overt hypertrophy	Replacement and diffuse interstitial fibrosis	Reduction of capillary density; vascular remodelling	Patchy distribution and great variation of disarray within the heart Altered calcium cycling and sarcomeric calcium sensitivity; impaired cardiac energy homeostasis	LV midwall; diffuse; patchy; RV insertion points	Increased native T1 even in the absence of LGE	Increased ECV due to fibrosis

Table 2 (continued)

Disease	Pathophysiological features				Tissue characterization		
	Extent/distribution of left ventricular hypertrophy	Fibrosis/extracellular matrix	Microcirculation	Disarray/cellular abnormalities	Late gadolinium enhancement	Parametric Mapping	Extracellular volume
Fabry disease	Concentric or asymmetric LVH Great contribution of LV papillary muscle mass to the total LV mass RVH In men, LVH consists mainly of increasing myocyte contractile protein In women, the LVH consists of balanced sphingolipid and myocyte hypertrophy in proportion	Fibrosis and inflammation mainly in the basal inferolateral wall In the late phase, extensive fibrosis occurs	Globotriaosylceramide deposition in vascular endothelium leads to endothelial dysfunction	Globotriaosylceramide accumulates in cardiomyocytes, conduction system cells, valvular fibroblasts, endothelial cells, and vascular smooth muscle cells	Initially, in the basal inferolateral wall LGE in LVH-negative subjects only occurs in women	Low native T1 Increased T2 reflects myocardial inflammation	Normal ECV, except for scarring regions
Pompe disease	Early infantile-onset form of Pompe disease presents severe In late-onset Pompe disease (LOPD) a minority of patients demonstrated mild LVH	Mild accumulation of glycogen Absence of significant fibrosis in LOPD		Accumulation of lysosomal glycogen in cardiomyocytes	Nonsubendocardial in the basal LV inferolateral wall Not frequent in children		
Danon disease	Concentric LVH	Interstitial myocardial fibrosis patchy and extensive in advancedstages		Accumulation of autophagic vacuoles in cardiomyocytes Hypertrophic muscle fibres	Patchy, subendocardial, midwall and transmural patterns. RV free wall	Increased native T1, at early stage Increased T2	
Neurodegenerative disorders—Friedreich's ataxia	Concentric LVH LV mass positively correlated with the GAA repeat number	Diffuse fibrosis Myocardial inflammation may be present as a precursor of overt cardiomyopathy	Microvascular disease due to impaired mitochondrial function. Frataxin deficiency has a direct effect on endothelial cells	Cellular hypertrophy Mitochondrial iron accumulation in cardiomyocytes	May be found in the absence of severe LVH	Absence of significant iron overload using T2* imaging, (localization of iron particles in the mitochondria)	

Table 2 (continued)

Disease	Pathophysiological features				Tissue characterization		
	Extent/distribution of left ventricular hypertrophy	Fibrosis/extracellular matrix	Microcirculation	Disarray/cellular abnormalities	Late gadolinium enhancement	Parametric Mapping	Extracellular volume
Malformation Syndromes RASopathies • Noonan • LEOPARD	Asymmetrical LVH Affection of LV and RV outflow tracts Right midventricular stenosis	Focal and interstitial fibrosis	Reduced myocardial perfusion due to the increased myocardial mass	Myocytes disarray	Focal	Increased T1	
Mitochondrial disease - MELAS - MERFF - CPEO - KSS	Concentric LVH, potentially with evolution to LV dilation and dysfunction More frequent in MELAS/-like patients	Disperse interstitial and replacement fibrosis Myocardial edema	Mitochondrial angiopathy and vasogenic edema	Diffuse cellular hypertrophy Intramitochondrial paracrystalline and lipidic inclusions	Intramural or subepicardial pattern in the inferolateral wall or septum Transmural extension may be presented LGE may precede LVH		
Pseudo-hypertrohy							
Amyloidosis	Symmetric or asymmetric LVH LV mass is higher ATTR amyloidosis compared with AL type	Proteins accumulate within interstitial space Myocardial edema associated with light chain or fibril toxicity	Endothelial dysfunction and impaired arteriolar reactivity	Light chains cause increase in cellular reactive oxygen species toxicity, lysosomal dysfunction and impaired calcium homeostasis	Global subendocardial; patchy; diffuse; transmural RV LGE is apparent in the majority of ATTR patients and in 70% of AL patients	Marked increased native T1 (AL CA > TTR CA) Increased T2, higher in AL	Marked increase ECV (AL CA < TTR AL)
Myocardial inflammation	Expansion of the extracellular space	Interstitial edema Infiltration of inflammatory cells Fibrosis	Myocardial vascular bed hyperemia; increased vascular permeability	Intracellular edema Loss of cell membrane integrity	Patchy, subepicardial and midwall. Frequently in the basal to mid-inferolateral wall. In severe inflammation, LGE is extensive through to the subendocardium	Increased native T1 Increased T2	Increased ECV

Additional references for Table 1 are provided in supplemental material

AL light chain amyloidosis, *ATTR* transthyretin amyloidosis, *CA* cardiac amyloidosis, *CPEO* chronic progressive external ophthalmoplegia, *ECV* extracellular volume, *GAA* guanine-adenine-adenine, *GH* growth hormone, *HTN* hypertension, *KSS* Kearns-Sayre syndrome, *IGF-1* insulin-like growth factor-1, *LGE* late gadolinium enhancement, *LOPD* late-onset Pompe disease, *LV* left ventricle, *LVEF* left ventricular ejection fraction, *LVH* left ventricular hypertrophy, *MELAS* mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke, *MERFF* myoclonic epilepsy with ragged-red fibers, *RV* right ventricle, *RVH* right ventricular hypertrophy

T1 and 37% for ECV showed high diagnosis accuracy) [79, 130, 131]. The very high values of T1 can be diagnostic in themselves, a benefit in those who may not receive contrast due to renal dysfunction. The pattern of LGE is globally subendocardial, becoming transmural with incremental amyloid accumulation. Gadolinium presents a characteristic kinetic pattern, since it is avidly taken up by the infiltrated myocardium [132–134]. Despite the differences between cohorts of patients with AL and ATTR amyloidosis, for an individual patient CMR alone does not allow an accurate differential diagnosis between the two types, although some aspects can point toward a specific type. Native T1 and T2 are higher in AL amyloidosis due to the direct cellular light-chain toxicity and consequent edema [79, 129]. On the other hand, ECV is higher and LGE substantially more extensive in ATTR [79, 133]. RV LGE is present in the vast majority of ATTR compared to AL patients [133]. When combined with negative monoclonal protein studies, characteristic LGE pattern indicative of cardiac amyloidosis is highly specific for the diagnosis of cardiac ATTR amyloidosis (specificity of 98% and positive predictive value of 99%), compared with endomyocardial biopsy [135]. In cardiac amyloidosis, parametric mapping may further provide prognostic information, as ECV quantifies disease severity and adds prognostic value [132], while T2 is higher in untreated AL compared with treated AL, constituting also a predictor of prognosis [129].

"Pseudo-hypertrophy" may be the presenting phenotype of acute myocarditis (Fig. 6), regardless of the aetiology. Myocardial inflammation is the result of a response to viruses, autoimmune disease or toxic agents [136]. Extracellular expansion is primarily characterized by the infiltration of inflammatory cells and interstitial edema, followed by collagen deposition, fibrosis and scar [136, 137]. The imaging equivalent of the inflammatory process consists of an increased T1 as result of intra and extra-cellular edema, hyperemia/capillary leak, necrosis and fibrosis; increased T2 due to myocardial edema/active inflammation; increased ECV reflecting extracellular edema, hyperemia/capillary leak, necrosis and fibrosis [138]. LGE also depicts areas of necrosis, fibrosis and extracellular edema, with a subepicardial and midwall pattern, frequently in the basal to mid-inferolateral wall [138]. In severe inflammation, LGE is extensive through to the subendocardium [138].

A unique cause of myocardial inflammation is cardiac allograft rejection [139] where variable degrees of LVH can occur. Endomyocardial biopsy is still the gold standard for the diagnosis, but a non-invasive approach using CMR has emerged as a relevant complement. Native T1, T2 and ECV were found to be elevated in patients with acute cardiac allograft rejection [140] as result of myocardial edema and fibrosis, important pathological markers of the condition [141]. Furthermore, T1 mapping showed to be able to track recovery after pulse immunosuppressive therapy [142]. Recently, a prospective randomized noninferiority pilot study compared a strategy based on CMR vs endomyocardial biopsy

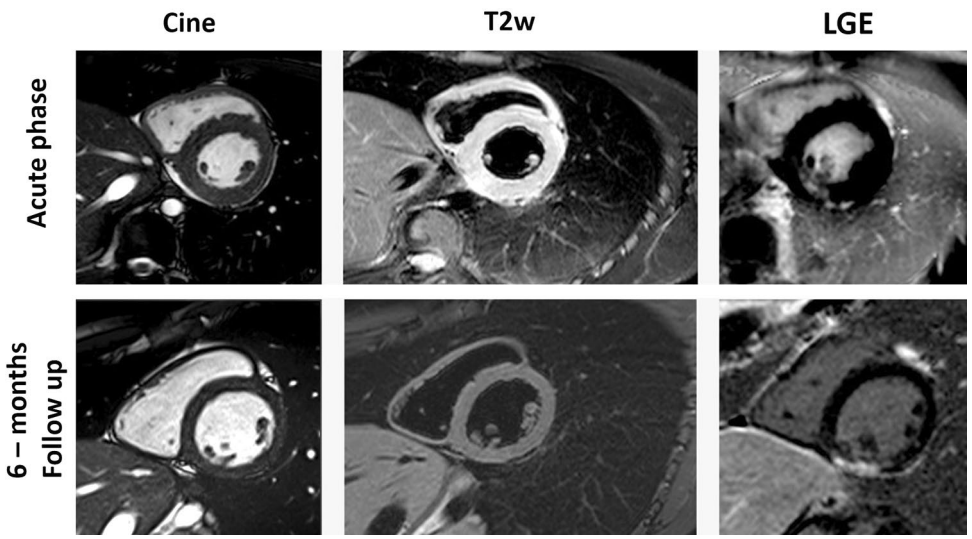

Fig. 6 Acute myocarditis. 20-year-old man with unremarkable previous medical history, presented with chest pain associated with inferior negative T waves on electrocardiogram and mildly increased troponin I. Cardiovascular magnetic resonance (CMR) showed concentric left ventricular (LV) hypertrophy (LV wall thickness 16 mm, LV mass 200 g), mildly impaired LV systolic function (LV ejection fraction 52%). On T2 weighted (T2w) imaging, myocardial signal was diffusely increased reflecting myocardial edema. Subepicardial to transmural late gadolinium enhancement (LGE) was noted in the LV mid-inferior wall. At 6 months follow up CMR showed normal LV wall thickness (9 mm); normal LV systolic function (LV ejection fraction 59%). Normal myocardial signal was documented on T2w. Transmural LGE persisted in the LV mid-inferior wall

for rejection surveillance, documented that CMR rejection surveillance was feasible in the first year after transplantation and reduced the number of invasive endomyocardial biopsy [143].

Conclusion

In an era in which imaging is being increasingly used, rational incorporation into the diagnostic process is mandatory. Identifying the true etiology of an apparent pathological process is the final aim, which allows for optimal therapeutic options and estimating prognosis. CMR is rapidly becoming a new gold standard for the assessment of LVH, but finds its rightful place only when adequately integrated in a rich clinical milieu. Due to the overlap of phenotypes between the distinct etiologies, CMR in isolation has evident limitations in differential diagnosis, performing better in diseases with severe tissue abnormalities.

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Declarations

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