

# Imaging of Left Ventricular Hypertrophy: a Practical Utility for Differential Diagnosis and Assessment of Disease Severity

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## Abstract

**Purpose of Review** Left ventricular hypertrophy (LVH) is often encountered in clinical practice, and it is a risk factor for cardiac mortality and morbidity. Determination of the etiology and disease severity is important for the management of patients with LVH. The aim of this review is to show the remarkable progress in cardiac imaging and its importance in clinical practice.

**Recent Findings** This review focuses on clinical features and characteristic cardiac imaging in LVH caused by various diseases including hypertension, aortic valve stenosis, hypertrophic cardiomyopathy, and secondary cardiomyopathies. The usefulness of echocardiography as a tool of general versatility including hemodynamic evaluation and the usefulness of cardiac magnetic resonance imaging for assessment of cardiac morphology and myocardial tissue characteristics of relevance for LVH are described.

**Summary** Imaging modalities now have central roles in the differentiation and prognostic assessment of LVH.

**Keywords** Left ventricular hypertrophy · Cardiac imaging · Echocardiography · Cardiac magnetic resonance · Cardiomyopathy

## Introduction

Left ventricular hypertrophy (LVH) is important clinically because it is prevalent and is associated with long-term prognosis including heart failure, arrhythmias, and death. LVH can be caused by various conditions or diseases, though hypertension and aortic stenosis are the major causes of LVH [1–4]. Figure 1 shows the prevalence and influenced age among the differential diagnosis of LVH. Various types of cardiac imaging are useful for detecting LVH. Furthermore, these modalities are indispensable for determining the etiology of LVH and for assessing the disease severity, which are important in clinical practice because accurate diagnosis and determination of the disease stage are linked to the treatment strategy. In this review paper, echocardiography and cardiac magnetic resonance (CMR) are mainly focused on because these two modalities play a key role in cardiology, particularly in assessment of LVH.

## Cardiac Imaging

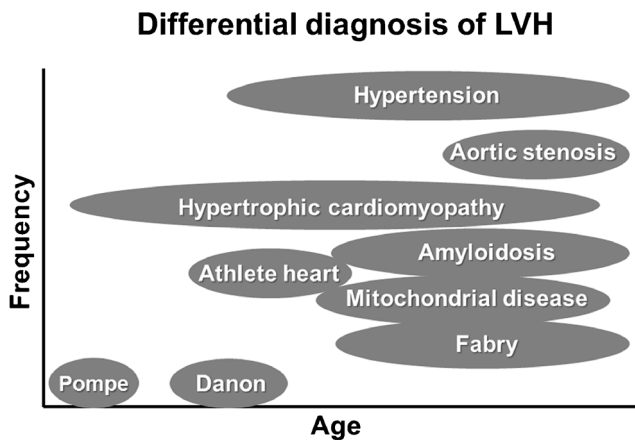
Table 1 shows disorders causing or associated with LVH and the features of cardiac imaging in those patients. Echocardiography is non-invasive and easily repeated, and it is the most frequently used technique for diagnosing cardiovascular diseases. Moreover, the hemodynamic state, which is closely associated with disease severity, can be evaluated by Doppler echocardiography. Recently, there have been remarkable developments in CMR imaging techniques, and CMR imaging has become a first-line modality for the assessment of cardiovascular diseases, particularly cardiomyopathies, because of its tomographic, high spatial resolution, and excellent contrast and it enables non-invasive tissue characterization. CMR imaging enables visualization and quantification of the

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**Fig. 1** The prevalence and influenced age among the differential diagnosis of LVH. *LVH* left ventricular hypertrophy

size, mass, and regional and global functions of both ventricles. Late gadolinium enhancement (LGE), which is considered to reflect myocardial scar and fibrosis, is being increasingly used in CMR imaging for evaluation of cardiomyopathies. LGE is useful for differential diagnosis and risk stratification for subsequent cardiac events.

### Hypertension

Cardiovascular diseases are common in the general population, and hypertension is one of the most important risk factors for those diseases. LVH is a relatively early manifestation and a common finding in patients with hypertension. LVH as a consequence of hypertension is associated with an increased risk of major cardiovascular events including heart failure, coronary heart disease, stroke, and sudden death [5–8].

Echocardiography is a more sensitive modality than electrocardiography for identifying the presence of LVH. Echocardiography is also useful for distinguishing the four patterns of LV geometry based on the relationship between LV cavity size and relative wall thickness: normal LV geometry, concentric LV remodeling, eccentric LVH, and concentric LVH [5]. This morphological assessment is important because specific types of LV geometry, i.e., eccentric LVH and concentric LVH, are associated with a marked increase in subsequent cardiovascular events [9, 10].

### Aortic Valve Stenosis

There are several causes of aortic stenosis (AS) including congenital bicuspid aortic valve, rheumatic valvular disease, and degenerative aortic stenosis with advanced age (most commonly seen). The number of patients with AS has been increasing as a result the aging society, and AS is the most common valvular heart disease. Various degrees of diffuse LVH caused by pressure overload are observed in patients with AS.

Echocardiography is the main modality for the diagnosis of AS and assessment of severity [11]. The important factors for assessment are valve anatomy including the number of leaflets; extent of calcification; leaflet motion; hemodynamics including transaortic systolic pressure gradient, concomitant aortic regurgitation, LV, and aortic sizes; and degree of LVH. For treatment of patients with symptomatic severe AS, although traditional surgical aortic valve replacement remains the gold-standard treatment, transcatheter aortic valve implantation (TAVI) has become an alternative treatment option for high-risk or inoperable patients, and this new therapeutic modality is now widely performed [12]. Accurate imaging assessment is necessary for decision-making regarding indication and procedure for patients undergoing TAVI [13]. Multidetector computed tomography (MDCT) has emerged as a key imaging modality for pre-procedural assessment of patients scheduled to undergo cardiac interventions [14]. There are several parameters that are necessary to be measured by MDCT imaging in patients scheduled for TAVI: (1) aortic valve: cuspidity, distribution, and extent of calcification; (2) aortic root: ST junction aortic diameter, sinus of Valsalva width, and height; (3) aortic annulus: aortic annulus short and long diameters, area, and circumference; and (4) access route: vessel diameter, calcification, and so on.

### Hypertrophic Cardiomyopathy

New definition and classification of cardiomyopathies have been provided by several organizations including the World Health Organization/International Society and Federation of Cardiology, the American Heart Association, and the European Society of Cardiology [15, 16••]. In the guidelines by the Japanese Circulation Society for the diagnosis and treatment of hypertrophic cardiomyopathy (HCM), HCM is defined as a cardiomyopathy resulting from mutations in sarcomere protein genes or other types of mutations or a cardiomyopathy not associated with any other storage disease or systemic disease affecting multiple organ systems [17]. Cardiac hypertrophy resulting from a storage disease or a systemic disease affecting multiple organ systems is classified separately from HCM into “diseases causing HCM-like conditions.” Of note, patients with LVH due to specific causes may respond well to specific treatment. HCM is a primary myocardial disorder with heterogeneous morphologic, functional, and clinical features. Most previous studies on this disease in which the subjects were patients selected mainly from largely tertiary referral centers showed a poor prognosis with an annual mortality rate of 3–6%; due largely to sudden cardiac death, recent studies in community-based cohorts in Western countries have suggested a more favorable prognosis than that suggested by results of previous studies. The three modes of HCM-related deaths are sudden cardiac death, heart failure, and stroke, which is usually embolic stroke associated

**Table 1** The features of cardiac imaging in patients with disorders causing or associated with LVH

Disease	Category	Imaging
Hypertensive heart disease	Hypertension	Echo: concentric LVH CMR: non-specific
Aortic stenosis	Valvular disease	Echo: valvular calcification and decreasing the opening, transaortic valve pressure gradient, concentric LVH MDCT: pre-procedural assessment for TAVI CMR: non-specific
Hypertrophic cardiomyopathy	Primary cardiomyopathy	Echo: usually ASH (also concentric, apical LVH), LVOT obstruction, SAM, mitral apparatus abnormality, apical aneurysm
	Unexplained LVH	
	Mainly sarcomere mutations	CMR: LGE in intra-myocardium (mainly at the junction of the right ventricle and the interventricular septum), mitral apparatus abnormality, apical aneurysm
Amyloidosis	Secondary cardiomyopathy	Echo: concentric LVH, biatrial dilatation, restrictive physiology, thickened inter-septum, granular appearance, pericardial effusion
	Amyloidosis	
	Mainly AL type and ATTR type	CMR: global subendocardial LGE, prolonged native T1 Tc-PYP scintigraphy: uptake in ATTR type
Mitochondrial disease	Secondary cardiomyopathy	Echo: concentric LVH
	Mitochondrial disease	CMR: non-specific, maybe different LGE pattern in different subtypes
Fabry disease	Secondary cardiomyopathy	Echo: predominant concentric LVH
	Lysosomal storage disease	CMR: LGE in basal infero-lateral segments in LV, shortened native T1
	GLA mutations	
Pompe disease	Secondary cardiomyopathy	Echo: concentric LVH
	Lysosomal storage disease	CMR: non-specific
	GAA mutations	
Danon disease	Secondary cardiomyopathy	Echo: concentric LVH
	Lysosomal storage disease	CMR: non-specific

LVH left ventricular hypertrophy, CMR cardiac magnetic resonance, MDCT multidetector computed tomography, TAVI transcatheter aortic valve implantation, ASH asymmetric septal hypertrophy, LVOT left ventricular outflow tract, SAM systolic anterior motion of mitral valve, LGE late gadolinium enhancement, Tc-PYP 99m Tc-pyrophosphate, ATTR transthyretin

with atrial fibrillation [18, 19]. One important pathophysiological feature of HCM is “LV diastolic dysfunction due to cardiac hypertrophy.” Left ventricular outflow tract (LVOT) obstruction which is observed at rest in about 30% of patients and with provocation in about 30% of patients is also an important pathophysiological feature because LVOT obstruction is associated with severe symptoms and clinical outcomes including sudden death and heart failure events.

Echocardiography is the most frequently used imaging modality for diagnosis of HCM and assessment of the hemodynamic state in patients with HCM [20]. A clinical diagnosis of HCM is made when an unexplained increased LV wall thickness  $\geq 15$  mm is imaged anywhere in the LV wall. Two-dimensional echocardiography should be performed to assess the pattern of cardiac hypertrophy. Although the most common location for LVH is the basal anterior septum to the anterior free wall and asymmetric septal hypertrophy (ASH)

is the most common type of morphologic pattern, distribution of LVH are variable in HCM, including apical and concentric LV thickening (the hypertrophy usually being symmetric in secondary disease) [21, 22]. The presence of systolic anterior motion (SAM) of the mitral valve and mitral apparatus abnormality are also evaluated by echocardiography [23]. Doppler echocardiography is useful for evaluating LV diastolic function and the presence/absence of left or right ventricular obstruction. When it is difficult for lesions to be visualized by echocardiogram, other imaging techniques such as MDCT and CMR imaging should be used to make a diagnosis based on a comprehensive assessment of the patient. These techniques are especially useful for identifying the hypertrophied area in the lateral free wall or posterior septum or most commonly the apical wall and apical aneurysm [20, 24]. CMR imaging is also used for assessment of LV outflow obstruction with SAM, mitral apparatus abnormality, and ventricular function as well as the distribution and degree of hypertrophy. In addition, LGE in HCM provides sufficient information regarding differentiation from secondary cardiomyopathies and risk stratification. Myocardial LGE is a common feature of HCM; 40–60% of HCM patients have some LGE at the midwall in the hypertrophied area, most commonly at the anterior and posterior RV insertion points [20, 24, 25]. The presence and extent of LGE are associated with NYHA class and LV function. In clinical practice, LGE imaging is an important tool for identifying the disease condition. Extensive LGE is associated with progression to “dilated” or “end-stage” phase characterized by LV systolic dysfunction, which has a poor prognosis [26]. Since myocardial fibrosis may provide an arrhythmogenic underlying substrate, LGE imaging has been expected as an additional prognostic factor for prediction of sudden cardiac



**Fig. 2** CMR imaging with LGE in a 64-year-old HCM patient. CMR cardiac magnetic resonance, LGE late gadolinium enhancement

death. Figure 2 shows extensive LGE in LV wall particularly anterior to antero-septal wall in a 64-year-old HCM patient with sustained ventricular tachycardia. A recent multicenter study showed that the extent of LGE was associated with the risk of sudden cardiac death events and that extensive LGE (15% or more of the LV mass) was an independent predictor of sudden cardiac death events, although there have been several arguments about the prediction of sudden cardiac death [27, 28, 29].

### Amyloidosis

Systemic amyloidosis is a progressive disease and frequently involves more than one organ [30]. Although various amyloid proteins have been reported, the three most causative amyloid deposits are of monoclonal light chain (AL), transthyretin (ATTR), and serum amyloid A (AA) types [31]. Cardiac involvement in amyloidosis is the most important prognostic factor, and the frequency and severity of cardiac involvement are different depending on the type of amyloidosis [32]. Amyloid cardiomyopathy usually manifests as heart failure and conduction system abnormalities. Clinically relevant cardiac involvement is associated with AL amyloidosis and ATTR amyloidosis. On the other hand, AA amyloidosis rarely causes heart problems. AL amyloidosis is caused by deposition of a protein derived from immunoglobulin light chain fragments as primary amyloidosis or in association with multiple myeloma. In ATTR amyloidosis, the amyloid protein includes wild-type (non-mutant, senile systemic amyloidosis) or mutated transthyretin (hereditary, familial amyloidosis). Correct diagnosis is important since specific treatments are now available. Specific treatments are peripheral blood stem cell transplantation or chemotherapy with several drugs including bortezomib for AL amyloidosis and liver transplantation or tafamidis, a small molecule stabilizer of the transthyretin tetramer, for familial amyloidosis.

Echocardiography is needed to evaluate the morphology and hemodynamic state in patients with cardiac amyloidosis. Typical findings of cardiac amyloidosis in echocardiography are a symmetric increase in LV wall thickness and the presence of diastolic dysfunction [33–35]. A granular sparkling appearance of the myocardium, thickened valve leaflets, and mild pericardial effusion may also be present. Pulsed-wave Doppler is clinically useful for assessing the diastolic abnormalities of this disease including mitral inflow pattern changes from abnormal relaxation to restrictive filling resulting from decreased LV compliance and increased left atrial pressure. CMR imaging is useful for assessment of morphology including hypertrophied right ventricle wall and thickened atrial septum. LGE in CMR imaging is useful for differentiating cardiac amyloidosis from other diseases causing LVH, and the distinctive LGE distribution is a global subendocardial enhancement in a non-coronary artery territory, sometimes being patchy or diffuse [36–38]. Regarding the prognosis for patients with systemic amyloidosis, LGE in CMR imaging was reported to be associated with increased risk of mortality



[39, 40]. Recently, native myocardial T1 mapping has been shown to be useful for tracking the disease in amyloid cardiomyopathies including AL amyloidosis and ATTR amyloidosis [41–43]. It was also shown that pre-contrast T1 mapping and post-contrast myocardial extracellular volume might be able to predict mortality in patients with AL cardiac amyloidosis [44]. <sup>99m</sup>Tc-pyrophosphate scintigraphy has recently attracted attention because this old method, which had been used for detecting the area of acute myocardial infarction, is now recognized to be remarkably sensitive and specific for imaging ATTR cardiac amyloidosis [45–47]. Although cardiac amyloidosis was considered to be rare, a recent clinical study using <sup>99m</sup>Tc-pyrophosphate scintigraphy showed that wild-type ATTR cardiac amyloidosis (senile systemic amyloidosis) was an underdiagnosed disease in many patients who had heart failure with preserved ejection fraction and LVH [48•].

### Mitochondrial Disease

Mitochondrial diseases have a large variety of clinical manifestations that result from abnormalities in mitochondrial DNA [49, 50]. In these diseases, organs with high-energy requirements such as the brain, heart, and skeletal muscle are predominantly affected because mitochondria are cytoplasmic organelles responsible for generating adenosine triphosphate by the process of oxidative phosphorylation. There are many types of mitochondrial disorders in terms of clinical presentations, and a certain degree of overlap exists among the phenotypic forms. Well-known types include mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), chronic progressive external ophthalmoplegia (CPEO) or Kearns-Sayre syndrome (KSS), and myoclonus epilepsy associated with ragged-red fibers (MERRFs). Diagnosis of mitochondrial diseases is very challenging because of the broad phenotypic heterogeneity. Cardiac manifestations in mitochondrial diseases are cardiomyopathies and conduction abnormalities [51–53].

Echocardiography is useful for assessment of cardiac involvement in patients with mitochondrial diseases. However, there are various cardiac phenotypes including HCM-like morphology, dilated cardiomyopathy like, and restrictive cardiomyopathy like, and it is therefore difficult to diagnose mitochondrial disease without typical extracardiac findings. There is little information on CMR imaging findings in patients with mitochondrial diseases. According to previous reports, CPEO/KSS patients typically show an intramural pattern of LGE in the basal inferolateral wall, whereas MELAS patients show overt concentric hypertrophy and a rather unique, focally accentuated, and diffusely distributed LGE. Patients with MERRF seem to have no particular findings [54, 55].

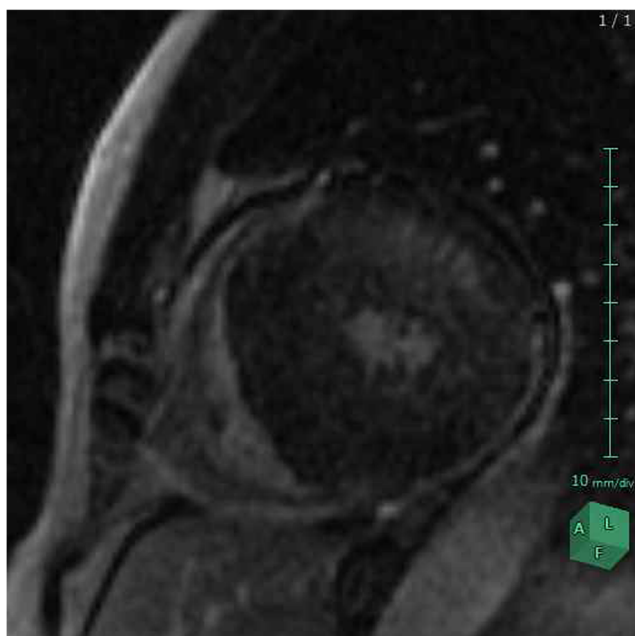
### Fabry Disease

Fabry disease is an X-linked lysosomal storage disease caused by mutations in the gene encoding the lysosomal enzyme  $\alpha$ -galactosidase A [56]. This enzymatic defect leads to progressive accumulation of glycosphingolipids, predominantly globotriaosylceramide and globotriaosylsphingosine, in lysosomes in multiple cell types throughout the body and causes multisystemic problems. Although Fabry disease is an X-linked disorder, most heterozygous females are now recognized to be affected [57]. Forms of Fabry disease include (1) the classic form of hemizygous males, (2) the late-onset form of hemizygous males, and (3) the form of heterozygous females. In male patients with the classic form of Fabry disease, symptoms are noted at a young age and there are various clinical manifestations including skin lesions, peripheral neuropathy, and renal involvement with proteinuria at a young age with progression to end-stage renal function. The majority of patients with this disease have cardiac involvement that is mainly manifested as LVH. In the late-onset form of male patients, a cardiac variant type presenting isolated cardiac manifestation has been recognized. Patients with this form have LVH after middle age without any other signs of Fabry disease [58]. Cardiac involvement of Fabry disease, either the classic form or a cardiac variant, is associated with significant morbidity and early death due to heart failure or arrhythmias. Enzyme replacement therapy (ERT) is now available for this disease [59].

Echocardiography shows LVH resembling HCM as an early cardiac abnormality, and the LVH pattern is usually diffuse concentric, though cases with asymmetric septal hypertrophy have also been reported [60]. A pressure gradient sometimes arises in the LV midventricle depending on the degree of hypertrophy. In the advanced stage of the heart, there is a decrease in ventricular wall motion with wall thinning, particularly at the base of the LV posterior wall [61]. In CMR imaging, concentric thickening is the most common morphology. In Fabry disease patients with some degree of LVH, LGE reflecting focal scarring is seen in the LV inferolateral wall of basal to midparts of the left ventricle [62, 63]. Figure 3 shows concentric LVH with LGE in the basal lateral wall in a 55-year-old man with Fabry disease. Recent studies have shown that native myocardial T1 mapping is useful for differentiating LVH patients: low T1 values in patients with Fabry disease and high T1 values in patients with amyloidosis [64, 65•].

### Pompe Disease

Pompe disease, glycogen storage disease type II, is an autosomal recessive lysosomal disorder with acid alpha-glucosidase (G AA) deficiency caused by mutations in the gene encoding lysosomal acid alpha-1,4-glucosidase [66].



**Fig. 3** CMR imaging with LGE in a 55-year-old man with Fabry disease. CMR cardiac magnetic resonance, LGE late gadolinium enhancement

GAA deficiency leads to accumulation of glycogen within lysosomes in tissues and is classified by age onset, organ involvement, and disease severity. The infantile form typically presents during the first few months of life and shows severe, generalized muscular hypotonia and cardiomyopathy with LVH. Without ERT, patients with the classic infantile form die in the first year of life from progressive cardiomyopathy [67, 68]. The late-onset form including childhood, juvenile, and adult onset is characterized by proximal muscular weakness and respiratory insufficiency without clinically significant cardiac involvement [69, 70].

There is insufficient information on cardiac imaging of infantile-onset Pompe disease because of the very young and severe conditions of patients. Congestive cardiac failure may be present due to impaired myocardial relaxation associated with gross hypertrophy. Delayed enhancement appears to be a rare finding by CMR imaging in this disease [71, 72].

### Danon Disease

Danon disease, glycogen storage disease IIb, is an X-linked lysosomal storage disease caused by mutations in the gene encoding lysosome-associated membrane protein 2 (LAMP2) [73, 74]. LAMP2 deficiency leads to the triad of cardiomyopathy, mild skeletal myopathy, and variable intellectual disability [75]. The age of onset ranges from childhood to adulthood. Men are severely affected, but female carriers also have a generally milder and later onset of disease. Elevated serum creatine kinase (CK) level is a useful clue for muscular dystrophies or metabolic disorders in cardiomyopathy, and Danon disease shows chronic hyperCKemia in all

male patients, even those without apparent muscle symptoms. At present, no specific treatment is available.

Echocardiography shows diffuse LVH with normal LV systolic function as the initial presentation before the age of 20 years in male patients and in adulthood in female patients. The cardiomyopathy progresses to LV systolic dysfunction, leading to refractory heart failure and death before the age of 30 years in males. Information on CMR imaging in patients with Danon disease is limited because of the rarity of the disease, but there have been several case reports [76, 77]. Concentric hypertrophy and LGE relatively sparing the septum may be characteristic imaging features of this disease.

### Conclusions

Cardiac imaging is now indispensable for the management of patients with LVH, and new techniques for cardiac imaging are continuing to be developed. The management of LVH should be decided on the basis of various cardiac imaging modalities in addition to biochemical markers and basic medical history-taking and physical findings.

### Compliance with Ethical Standards

**Conflict of Interest** Toru Kubo and Hiroaki Kitaoka declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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