**Update on left ventricular hypertrophy**

**Summary**
Detection and evaluation of left ventricular hypertrophy of unknown etiology by echocardiography is important in every cardiology practice. Causes of left ventricular hypertrophy include sarcomeric protein disorders (classical hypertrophic cardiomyopathy), metabolic disease (glycogen storage disease including LAMP2 deficiency, PRKAG2 mutations, Fabry disease), syndromic hypertrophic cardiomyopathy (Noonan’s syndrome, LEOPARD syndrome, etc.) and miscellaneous causes including systemic hypertension, amyloidosis, athlete’s heart and pheochromocytoma. Although there are several echocardiographic changes quite typical for some of the disorders, most changes are not 100% specific. ECG findings and symptoms provide important additional information. Genetic testing is increasingly important. Nowadays, a combination of ECG findings, symptoms, family history, genetic testing and findings of echocardiography provide the best means for differentiation of left ventricular hypertrophy.

**Introduction**
Assessment of presence and diagnostic evaluation of possible etiology of left ventricular hypertrophy (LVH) is a frequent problem in our daily cardiology practice. The prognostic implications of the various causes of LVH vary. Due to the frequent occurrence of LVH with or without a history of systemic hypertension, exact guidelines for further work-up are needed. In many patients, we do not investigate LVH further and assume it is due to hypertensive heart disease and might thus miss secondary causes. It is pertinent to exclude prognostic important forms of LVH such as hypertrophic cardiomyopathy (HCM) or amyloid heart disease and not to miss rare causes such as glycogen storage diseases.

An excellent article on the evaluation of severe LVH of unknown etiology was recently published by Elliott and McKenna [1]. The authors categorised causes of hypertrophic cardiomyopathy as follows: it can either be due to sarcomeric protein disease, metabolic disease, hypertrophy due to syndromic hypertrophic cardiomyopathy and, as a fourth group, miscellaneous disease. A slightly modified version of their classification is shown in table 1.

**Sarcomeric protein disease**
Hypertrophic cardiomyopathy is a sarcomeric protein gene disorder with autosomal dominant inheritance. It has been described in the mid 19th century by two pathologists [2, 3]. HCM occurs in 1 of 500 adults in the population [4]. HCM may be defined as left and/or right ventricular hypertrophy of unknown cause, which is usually, but not always, asymmetrical and associated with microscopic evidence of myocardial fiber disarray [5]. Nowadays, more than 200 mutations in 10 different genes are known [6]. Genetic testing in patients with suspected familial HCM is recommended and often performed – although we are not fully aware yet of the legal consequences regarding insurance policies and the psychological impact. The likelihood that a genetic mutation is detected in one of the genes that encode different components of the sarcomere is about 60%. Those patients in whom no mutation is detected may have another mutation or nonsarcomeric disease.

Up until now, unexplained LVH was the main diagnostic criterion for HCM with typically asymmetric hypertrophy and septal thickness greater than thickness of the free wall.
Left ventricular wall thickness in HCM may range from 13 to 60 mm. The echocardiographic picture of HCM is variable and extent and distribution of LVH may differ widely among patients with HCM [7]. In a large study group of 600 patients ranging from 7 to 79 years, multiple patterns of asymmetric LVH were identified. The anterior portion of the ventricular septum was the region of the left ventricle that most commonly showed thickening (96%) and was also the predominant site of hypertrophy in most patients (83%) [7]. Concentric wall thickening or wall thickening confined to the apex was rare occurring in 1% each in this study group [7].

30–50% of patients with HCM present with obstruction across the left ventricular outflow tract [4].

Not in all patients with genetically proven HCM, we find LVH. Therefore, it was also tried to detect preclinical HCM. One study attempted to detect the genotype in patients with preclinical HCM and β-myosin heavy chain mutations by tissue Doppler imaging [8]. An early diastolic annular velocity of less than 13.5 cm/s had a specificity of 86% and a sensitivity of 75% for identifying genotype positive subjects. If the combination of an annular E velocity of <15 cm/s with an ejection fraction of >68% was used, then the specificity was 100% [8].

### ECG changes in HCM

The ECG in HCM is abnormal in 75 to 95% of patients [9]. There is a wide variety of possible patterns. The ECG may be normal in mild degrees of LVH or show LVH and strain in the presence of extensive hypertrophy [9, 10]. Abnormal Q waves may mimic myocardial infarction and reflect septal hypertrophy whereas giant negative T waves are typical of apical HCM [5]. No particular ECG pattern reliably discriminates patients with or without obstruction in the left ventricular outflow tract or at risk of sudden cardiac death [9]. There is only a modest correlation between the extent of LVH and the ECG voltage [9]. No ECG pattern is specific or characteristic of HCM. To better demonstrate this, in figures 1A to 1D, an ECG of a patient with HCM is shown in comparison to a patient with amyloid heart disease, Fabry disease or hypertensive heart disease. None of the ECGs shows changes which would reliably allow diagnosis of the underlying disease.

### Metabolic disorders including glycogen storage disease

Metabolic disorders included are shown in Table 1. The most typical disorders in which myocardial thickening is caused by pathologic vacuoles containing glycogen or intermediary metabolites occur in Pompe’s disease (lysosomal acid α-1,4-glucosidase deficiency), Danon’s disease (X-linked lysosome-associated membrane protein LAMP2 deficiency), and Fabry disease.

Fabry disease which is an inherited deficiency of the enzyme α-galactosidase A has recently become more popular as new and nearly curative treatments with enzyme replacements have become available. α-galactosidase deficiency leads to glycosphingolipid accumulation in many organs including skin, kidney and heart. Most patients with Fabry disease have concentric LVH, and rarely asymmetrical septal hypertrophy [11, 12]. Typically in Fabry disease, there is diastolic dysfunction, systolic dysfunction occurs rarely. Valvular thickening is also frequent. In certain studies, up to 4% of...
patients referred with presumed HCM, Fabry disease was found [13]. Among Fabry patients, 6.3–9.7% present with nonobstructive HCM. In contrast, in a study of 100 patients who had symptomatic obstructive HCM and who underwent myectomy at the Mayo Clinic, in no patient there were signs of Fabry disease at histological examination [14].

A recently published study showed that in patients with LVH of unknown etiology in 40 of 75 patients (53%), sarcomeric mutations were found [15]. In none of the other 35 patients, there was Fabry disease or Pompe’s disease but in 3 (9%) patients with massive LVH and electrophysiological abnormalities, PRKAG2 and LAMP2 mutations were found. PRKAG2 gene regulates the Y subunit of AMP-activated protein kinase, it leads to glycogen filled vacuoles without myocardial disarray and without fibrosis. LAMP2 mutations (Danon’s disease) cause typically multisystem glycogen-storage disease but can also present rarely as a primary cardiomyopathy. In LVH of unknown etiology, Pompe has rarely to be considered as it is so pleiotropic; however, Fabry disease, LAMP2 and PRKAG2 mutations have to be considered. If a patient has massive LVH and signs of preexcitation in the ECG, then a mutation for LAMP2 or PRKAG2 are found in 46% of patients [15]. In Fabry disease, a short PR interval is also typical, additionally, we found in our own study (Hoigné et al, manuscript in preparation), that also a relatively short QTc interval is typical of Fabry disease.

**Syndromic hypertrophic cardiomyopathy**

Several genetic cardiomyopathies with LVH have been described in syndromes, such as in Beckwith-Wiedemann syndrome, Leopard syndrome, Noonan syndrome, and Friedreich’s ataxia [16].

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**Figure 1**

Different ECG examples of hypertensive heart disease, amyloid heart disease, hypertrophic cardiomyopathy and Fabry disease.

A ECG example of hypertensive heart disease in a 58-year-old female with normal coronary arteries and long standing severe hypertension. The repolarisation abnormalities disappeared within 6 months after antihypertensive therapy.

B ECG example of a 48-year-old male with amyloid heart disease due to multiple myeloma. There is no low voltage in the anterior leads as expected in amyloid heart disease.
Leopard syndrome (multiple lentigines syndrome) is a rare, autosomal dominant disorder with lentigines (L) with truncal and mucosal spots and larger café-au-lait spots, E for ECG changes, ocular (O) hypertelorism or widely spaced eyes, P for pulmonary valve stenosis, A for abnormalities of genitalia, R for retardation of growth and D for deafness [16]. It is a disorder of neural crest origin like pheochromocytoma, tuberous sclerosis and neurofibromatosis. Pulmonary stenosis is the most frequent cardiac abnormality, followed by myocardial hypertrophy with marked increased thickness of left ventricular septum and posterior wall, marked obstruction of left ventricular outflow tract and endocardial fibroelastosis [16].

Friedreich’s ataxia – the most common hereditary ataxia – is an autosomal recessive disorder, there is myocardial involvement in 95% [16]. Rarely, cardiac involvement can cause symptoms prior to neurological symptoms. The echocardiographic features include concentric LVH, normal systolic function, and thickened papillary muscles [16]. In other ataxic disorders there is no cardiac involvement.

**Miscellaneous causes**

The most common etiologies in this group are hypertension, athlete’s heart and amyloidosis. LVH in hypertension is typically present with concentric remodeling; it is rare that wall thickness of >1.5 cm occurs in patients with
In an excellent study, patients with HCM, hypertensives and athletes were compared [17]. In patients with HCM, asymmetrical septal hypertrophy (defined as septum to posterior wall ratio of 1.5:1) was found in 56%, in hypertensive in 18% and in 22% athletes. If one would take a ratio of 1.3:1 as some studies do as a diagnostic criterion for HCM, then ASH occurs in up to 44% of normal subjects, 42% of athletes and 30–70% of those with secondary hypertension, therefore, the ratio of 1.5:1 is more specific. In Shapiro’s study, distal ventricular hypertrophy was only found in patients with HCM, however, in only 10% [17]. Symmetrical LVH was demonstrated in 45 patients (34%) with HCM, 82% hypertensives and 78% athletes. The pattern of symmetrical LVH was therefore significantly more common in patients with secondary LVH. Overall, however, the pattern of hypertrophy was only moderately predictive in differentiating primary from secondary left ventricular hypertrophy. Wall thickness of exceeding 2 cm was not found in any athlete and in only 4 of 50 hypertensive patients but 40% of those with HCM.

The main discriminative features differentiating athlete’s heart from HCM include: unusual pattern of LVH, left ventricular cavity measuring less than 46 mm at end-diastole, abnormal left ventricular filling and familial HCM favor HCM. In contrast, a left ventricular cavity of more than 54 mm and a decrease in left ventricular wall thickening with deconditioning favor athlete’s heart [9]. The upper limit of “physiologic” wall thickening in highly trained athletes is 15–16 mm [19].

In pheochromocytoma, there are different echocardiographic features: rarely, it can resemble HCM, then apical cardiomyopathy, diffuse LVH, catecholamine induced myocarditis or dilated cardiomyopathy [20]. Contrarily to what one might expect, in one study, only 24 of 63 patients undergoing adrenalectomy for pheochromocytoma had an abnormal preoperative echocardiography [21].

Typical echocardiographic features of amyloid heart disease which is also called “stiff heart syndrome” includes increased left ventricular wall thickness, myocardial granular sparkling, normal left ventricular size, mild left atrial dilatation, pericardial effusion, valve thickening, diastolic dysfunction, decreased annular E wave and an abnormal strain rate [22, 23]. Diastolic dysfunction is an early sign of amyloid heart disease. Early forms of amyloid heart disease do not have a restrictive filling pattern, but can start with a nonspecific relaxation abnormality. Koyama
examined tissue Doppler imaging and strain rate imaging in patients with amyloid heart disease with and without heart failure [24]. Only in patients with heart failure, peak systolic velocity and peak A velocity were decreased, only E velocity is significantly lower in the posterior wall and basal segments of the 4 chamber view in all patients with amyloid heart disease. E velocity of less than 12 laterally and less than 10 cm/s medially was the best discriminator for the diagnosis of amyloidosis from controls. However, in amyloid heart disease, there is no finding which is absolutely specific of the disease. In figure 2, there is an example of a patient with amyloid heart disease due to multiple myeloma.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison of hypertensive heart disease, amyloid heart disease, hypertrophic cardiomyopathy and glycogen storage disease.</th>
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</thead>
<tbody>
<tr>
<td>hypertension heart disease</td>
<td>amyloid heart disease</td>
</tr>
<tr>
<td>LVH</td>
<td>yes</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>frequent</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>very rare</td>
</tr>
<tr>
<td>Increased echogenicity</td>
<td>occasionally</td>
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<tr>
<td>Valvular thickening</td>
<td>occasionally</td>
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<tr>
<td>Anomalous papillary muscle</td>
<td>rare</td>
</tr>
<tr>
<td>Short PR interval</td>
<td>rare</td>
</tr>
<tr>
<td>Genetic testing</td>
<td>not recommended</td>
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</tbody>
</table>

The differentiation of hypertensive heart disease (HHD) from HCM can be difficult. In the example in figure 3, the echocardiographic 2D image of a patient with longstanding hypertension is shown. Just by 2D echocardiographic features alone it is impossible in many patients to discriminate HHD from HCM. The prognostic implications are enormous, however. The ratio of the interventricular septum to the posterior wall is typically ≥1.3 in HCM. However, in many patients with HCM, the ratio can be less with a considerable overlap between HHD and HCM. Symmetrical hypertrophy does not exclude HCM, 13–31% of the patients with HCM have exactly this picture. In these patients, strain rate imaging may be able to help to differentiate [25]. There are many studies which attempt to find the best parameter to differentiate HHD and HCM. In a study by Oki from 2004 he attempted to differentiate HHD, HCM or cardiac amyloidosis with tissue Doppler imaging. Only in patients with advanced amyloid heart disease, differentiation was possible [26]. Therefore, we do not have a good echocardiographic test to reliably diagnose early forms of cardiac amyloidosis.

In our own recent retrospective study by Hoigné et al. (manuscript in preparation), we tried to differentiate Fabry disease from amyloid heart disease, HCM and hypertensive heart disease by integrating ECG findings, symptoms and echocardiographic findings. The most helpful signs were as follows: papillary muscle abnormalities for HCM, pericardial effusion and orthostasis/syncope for amyloidosis, hypertension for hypertensive heart disease and polyneuropathy for Fabry disease. The papillary muscle abnormalities in HCM...
involve direct continuity of the anterolateral papillary muscle with the anterior mitral leaflet, anterior displacement of the papillary muscle [27, 28]. A summary of the results is shown in table 2. Diastolic dysfunction, increased echogenicity and valvular thickening are not specific and can occur in any etiology of left ventricular hypertrophy. A short PR time is very typical of glycogen storage disease. In figure 4 there is an example of a patient with a more atypical nonobstructive HCM with normal interventricular septal wall thickness but negative T waves in the ECG and thickening of posterior wall and apical segments.

Pseudo left ventricular hypertrophy

In figure 5, the example of a 43-year-old man with normal blood pressure is shown who developed within one week “left ventricular hypertrophy” as shown in these M-mode images. He had advanced HIV infection with severe Pneumocystis carinii pneumonia. Viral myocarditis was assumed; he died suddenly two weeks later. Reversible “hypertrophy” due to myocardial edema has also been reported in myocarditis, Tako-Tsubo cardiomyopathy, and after heart surgery or transplantation due to myocardial reperfusion injury [29, 30].

Figure 5
Example of a patient with pseudohypertrophy of the left ventricle due to assumed viral myocarditis. Myocardial thickening was not present seven days prior to the next echocardiographic examination (A) but was severe after seven days (B).

Conclusion

Differentiation of unexplained LVH by echocardiography and also by including modern methods including tissue Doppler imaging and strain rate imaging is difficult. There are only rarely specific criteria which frequently apply in advanced disease only. Family history, ECG and symptoms are helpful. The role of genetic testing will be increasingly important.

References

7 Kluess HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. J Am Coll Cardiol 1995;26:1699–708.