



# Common presentation of rare diseases: Left ventricular hypertrophy and diastolic dysfunction

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## ARTICLE INFO

### Article history:

Received 27 October 2017

Received in revised form 14 December 2017

Accepted 2 January 2018

### Keywords:

Left ventricular hypertrophy  
Hypertrophic cardiomyopathy  
Myocardial storage  
Anderson Fabry disease  
Danon disease  
Amyloidosis

## ABSTRACT

Left ventricular hypertrophy may be a consequence of a hemodynamic overload or a manifestation of several diseases affecting different structural and functional proteins of cardiomyocytes. Among these, sarcomeric hypertrophic cardiomyopathy (HCM) represents the most frequent cause. In addition, several metabolic diseases lead to myocardial thickening, either due to intracellular storage (glycogen storage and lysosomal diseases), extracellular deposition (TTR and AL amyloidosis) or due to abnormal energy metabolism (mitochondrial diseases). The recognition of these rare causes of myocardial hypertrophy is important for family screening strategies, risk assessment, and treatment. Moreover, as there are specific therapies for some forms of HCM including enzyme substitution and chaperone therapies and specific treatments for TTR amyloidosis, a differential diagnosis should be sought in all patients with unexplained left ventricular hypertrophy. Diastolic dysfunction is a key feature of HCM and its phenocopies. Its assessment is complex and requires evaluation of several functional parameters and structural changes. Severe diastolic dysfunction carries a negative prognostic implication and its value in differential diagnosis is limited.

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## 1. Definition of left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is usually defined as an increase in left ventricular (LV) mass. However, in the last three decades there has been a longstanding debate on the thresholds defining normal ranges and the pathological myocardial hypertrophy [1,2]. Proposed limits or cut-off values differ according to age, sex, body build, ethnicity and investigational methods. While echocardiography (ECHO) remains the most frequent method for LV mass assessments, cardiac magnetic resonance (CMR) is now considered to be the reference standard. The main disadvantage of ECHO include limited image quality in a non-negligible proportion of patients and the use of geometric models to compute the LV mass that assume homogenous distribution of myocardial thickening (a problem in HCM as hypertrophy is often asymmetrically distributed). Another universal limitation is the need to adjust the measurements to the body build of the patient. Several methods used in the literature reflect our incapacity to find a simple and universally applicable method suitable for all individuals. The use of body surface area

(BSA), height or different indexes derived from height (e.g. height<sup>2.7</sup>) are frequently used. However, different methods may lead to discordant conclusions particularly in obese or heavily muscled individuals [3,4]. In children growth substantially influences the cardiac muscle mass and the measurements should be assessed as a deviation from predicted mean values (LV hypertrophy is usually based on the finding of z-score > 2, z-score being defined as a number of standard deviations from the population mean) [5,6].

In addition to left ventricular mass, LV remodelling should be taken into consideration as LV mass may be elevated in both dilated hearts (eccentric LV hypertrophy) and in hearts with small or normal cavity sizes due to wall thickening alone (concentric LV hypertrophy). In most patients with metabolic cardiomyopathies the hypertrophy is rather diffuse and usually concentric (with an increase in LV relative wall thickness). However, as in sarcomeric HCM, remodelling can have a nonuniform distribution with predominant septal or apical distribution [7].

Due to all these limitations and to the fact that pathological hypertrophy is not necessarily homogenous, the definition of hypertrophic cardiomyopathy (HCM) does not rely on LV mass measurements. Instead maximum wall thickness exceeding a threshold value in one or more myocardial segments is used. Based on 2014 ESC guidelines, HCM is defined by the presence of increased LV wall thickness that is not solely explained by abnormal loading conditions. Wall thickness of

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$\geq 15$  mm measured by any imaging technique (echocardiography, CMR or computed tomography) is required for the diagnosis. However, the guidelines acknowledge that many genetic and non-genetic disorders can present with lesser degrees of wall thickening (13–14 mm). In these cases, the diagnosis of HCM requires evaluation of other clinical and laboratory features and multi-modality cardiac imaging [8].

In daily clinical practice, patients fulfilling diagnostic criteria for HCM should undergo an appropriate workup according to current guidelines. The situation can be different in patients with milder degrees of LVH, who often escape a thorough diagnostic process and are either wrongly labelled as hypertensive heart disease or the finding remains simply unexplained. Vice versa in elite athletes, mild physiological hypertrophy often provokes a laborious process of differential diagnosis between “athlete’s heart” and HCM. This approach is justified if LVH is substantial (e.g. wall thickness  $\geq 14$  mm), inappropriate to the degree of training or type of sport, in presence of signs of diastolic dysfunction, any significant symptom (e.g. chest pain, unexplained shortness of breath, palpitations, syncope) or family history of heart failure (HF) or sudden cardiac death (SCD) before age of 45 years [9,10].

## 2. Diastolic dysfunction

In most patients with sarcomeric and non-sarcomeric HCM ejection fraction (EF) remains within normal ranges. However, decreased systolic function may be observed in many metabolic disorders and in advanced stages of sarcomeric HCM (sometimes referred to as the ‘burnt-out’ or hypokinetic dilated phase) [11,12]. Metabolic diseases prone to rapidly progress to systolic dysfunction include mitochondrial cardiomyopathies, Danon disease and to some degree amyloidosis [13, 14]. Nevertheless, in the large majority of HCM patients early signs and symptoms of HF are due to diastolic dysfunction, if significant mitral regurgitation and/or left ventricular outflow tract (LVOT) obstruction are absent.

Diastolic dysfunction accompanies a large spectrum of cardiac diseases and impairment of LV filling is the leading cause of dyspnoea and decreased exercise capacity. Lacking any specific diagnosis, symptomatic patients with normal or borderline EF are labelled as HFpEF or HFmrEF (heart failure with preserved/mid-range EF). According to current guidelines, the following criteria should be met: elevation of natriuretic peptides (NPs) (BNP  $> 35$  pg/mL and/or NT-proBNP  $> 125$  pg/mL), structural alterations of the left heart including LVH (defined as LV mass index  $\geq 115$  g/m<sup>2</sup> for males and  $\geq 95$  g/m<sup>2</sup> for females) and/or left atrial volume index (LAVi)  $> 34$  mL/m<sup>2</sup> and the presence of ECHO criteria of diastolic dysfunction [15].

This approach may mislead physicians to simple conclusions that HFpEF or HFmrEF represent a final diagnosis, which is not the case. Several pitfalls to this approach should be noted. First, the cut-off values for natriuretic peptides are set relatively low and should be used to exclude the possibility of HF diagnosis rather than to confirm it. Even in patients with mild HCM a slight elevation of NPs may be present.

Second, the issue of LVH diagnosis should be taken into consideration. Universally applicable cut-off values using BSA index as allometric correction factor will underestimate the presence of LVH in obese patients [1]. The proposed cut-off values are relatively low. A large proportion of patients have values close to the limit and due to the lack of accuracy of routine ECHO measurements may be wrongly labelled as having LVH [16]. In contrast, the use of LV mass often derived from linear measurements including the septum and posterior wall thickness and internal LV cavity dimension may lead to a missed diagnosis of localized myocardial thickening for example, at the apex.

Third, the wide spectrum of ECHO measures used for the assessment of diastolic function reflect the complexity of the task and inability of a simple parameter to make a precise diagnosis. In addition, recently issued recommendations for heart failure diagnosis and evaluation of diastolic function differ and may be misleading [15,17].

## 3. Physiological LVH and diastolic function

Diastolic dysfunction is common in patients with LVH and in many cases signs of impaired LV filling precede the development of overt LVH. The only exception from this common scenario is represented by individuals with physiological cardiac adaptational changes induced by physical training. Most athletes have normal or supranormal diastolic filling parameters except for atrial dilatation which is often seen in highly trained athletes. In some athletes ECHO parameters may reveal borderline values leaving the question of “physiologic” character of hypertrophy open and additional investigation may be needed [8,9,18].

## 4. Assessments of diastolic dysfunction in patients with HCM

Various complex echocardiographic evaluations of diastolic function have been proposed for patients with preserved systolic function. Suggested parameters include septal and lateral  $e'$  velocity measurement by tissue Doppler imaging (TDI),  $E/e'$  assessment, LAVi measurement and evaluation of tricuspid regurgitant velocities (Fig. 1) [17]. Although these indices are suggested as essential, a large number of other parameters may be used including mitral and pulmonary venous flow evaluation, IVRT measurement, Valsalva manoeuvre, and the time interval between the onset of E and  $e'$  and others.

In HCM patients the evaluation is even more complicated and data supporting the reliability of different diastolic indices weaker. The phenotype in sarcomeric HCM is extremely variable, even in the presence of the same mutation and individual patients differ with respect to the degree and distribution of myocardial hypertrophy, myocyte disarray, fibrosis extent, presence or absence of LVOT obstruction, and left atrial structure and function. In most patients the changes in Doppler indices are influenced by both impaired relaxation and compliance making them difficult to interpret. This may be even more pronounced in metabolic cardiomyopathies caused by intracellular storage (Anderson Fabry or Danon disease) or extracellular deposits (amyloidosis) (Fig. 1) [17, 19].

The evaluation of LV filling in HCM therefore requires an integrative approach taking into account mainly  $E/e'$  ratio, LAVi, pulmonary venous flow analysis with assessment of flow atrial reversal velocity and duration, and assessment of tricuspid regurgitant flow velocity as an indirect measure of pulmonary hypertension. The restrictive filling pattern with high E/A and  $E/e'$  ratios and left atrial dilatation carries a negative prognostic implication regardless of the underlying process. It should be kept in mind that some cardiomyopathies traditionally considered as exemplars of restrictive cardiomyopathy (e.g. amyloidosis) do not necessarily have the typical restrictive filling pattern particularly in the early stages of disease [17,20].

## 5. Rare diseases and HCM

Clinically defined HCM represents a relatively common condition with a prevalence ranging from 0.02% up to 0.23% in adults. In up to 60% of adolescents and adults the disease is caused by an autosomal dominant trait due to mutations in cardiac sarcomere protein genes. About 5 to 10% of HCM cases are caused by rare inborn errors of metabolism. In the elderly up to 10% may result from non-genetic diseases such as senile wild-type TTR amyloidosis or AL amyloidosis. Some of the rare metabolic diseases may have systemic manifestations (such as renal, neurological or neuromuscular or cutaneous) [8,21].

There are several reasons why it is important to make a timely and correct diagnosis of these rare conditions. Treatment may be substantially different from that used to manage sarcomeric HCM. In some diseases such as Anderson-Fabry (AFD) or Pompe diseases specific treatments have been developed and approved for clinical use [22]. For others such as TTR amyloidosis targeted treatments are in advanced stages of clinical development [23]. Most metabolic diseases are progressive with higher risk of complications in older patients. Their

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