HCM and its Multiple phenotypic expression classifications

I) **Genotype-positive and phenotype-negative HCM, Subclinical HCM "Near Normal variant"**

Related to relatives of individuals' genetic mutation for HCM, or those who should be followed up for the risk of developing any other variant such as the presence of crypts: genotype-positive and phenotype-negative HCM (***Captur G, et al.* Prediction of sarcomere mutations in subclinical hypertrophic cardiomyopathy. *Circ Cardiovasc Imaging. 2014 Nov; 7(6): 863-71***), abnormal trabeculation, and anterior mitral valve leaflet elongation. Some studies have pointed at the presence of myocardial crypts (ie, narrow, blood-filled invaginations within the LV wall) as a prephenotypic marker of HCM in the absence of LVH.

LV myocardial crypts represent a distinctive morphological expression of HCM, occurring with different frequency in HCM patients with or without LVH. Crypts are a novel CMRI marker, which may identify individual HCM family members who should also be considered for diagnostic genetic testing. These data support an expanded role for CMRI in early evaluation of HCM families. Single or paired inferobasal myocardial crypts were an occasional and by no means rare finding among patients referred for CMRI without a pretest suspicion of HCM. This, together with similar previous findings in a cohort of healthy volunteers, supports their being regarded, in such individuals, as incidental

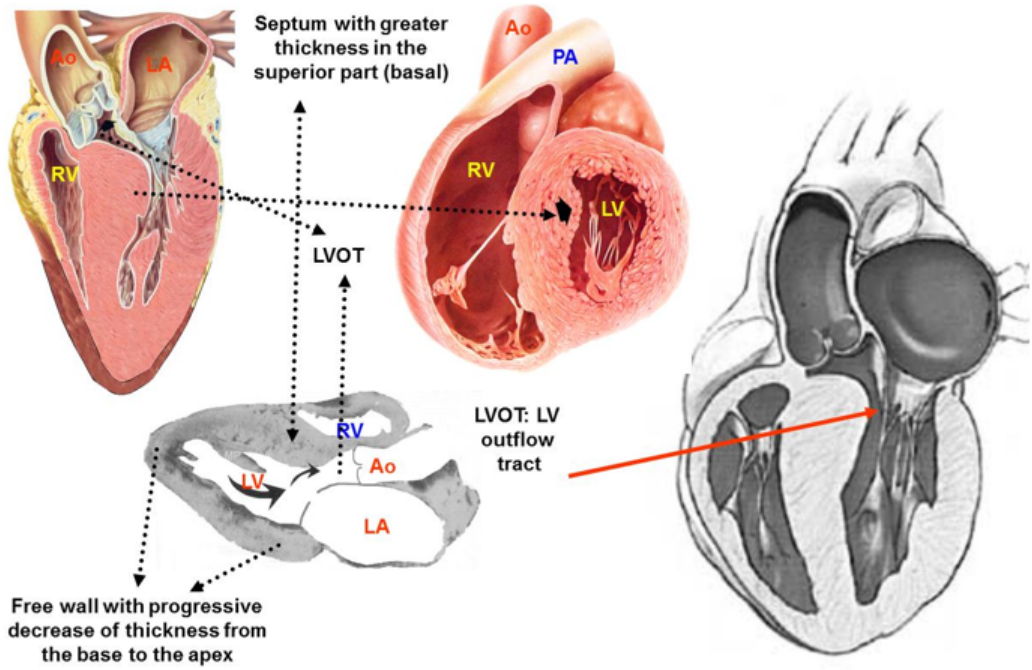
variants of local myocardial structure, unlikely to require further investigation. It is necessary a larger registry-type study may be justified to investigate the clinical implications of multiple crypts, especially if associated with HCM family history. **(Petryka J, Baksi AJ, Prasad SK, *et al.* Prevalence of inferobasal myocardial crypts among patients referred for cardiovascular magnetic resonance. Circ Cardiovasc Imaging. 2014;7:259-264**.) Phenotype negative HCM suggest that HCM is more common than previously estimated, which may enhance its recognition in the practicing cardiovascular community, allowing more timely diagnosis and the implementation of appropriate treatment options for many patients. (**Christopher Semsarian, et al. New perspectives on the prevalence of hypertrophic cardiomyopathy. J Am Coll Cardiol. 2015 Mar 31;65(12): 1249-1254. doi: 10.1016/j.jacc.2015.01.019**.).

II) **Septal asymmetrical variant with resting LVOTO and "S" shape or sigmoid septum (obstruction at subaortic level):**

This variant is the most frequent and is found in approximately 20% of the patients and is associated with mitral valve SAM and mitral regurgitation. Sigmoid septum (focal and isolated hypertrophy of the basal interventricular is defined as a septum≥13mm in men and ≥12mm in women, exceeding ≥50% of the median septum thickness) was classified as «Type 1» (≤14mm) and «Type 2» (≥15mm). Regarding the HCM,

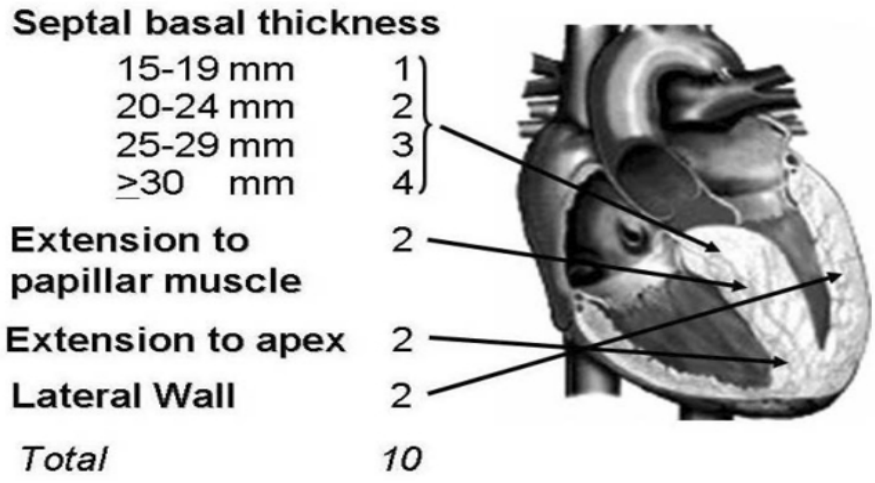
patients with type 2 sigmoid septum are older and generally hypertensive; otherwise, often they have no clear differences in their clinical, ECG or TTE characteristics. Therefore, CMR is helpful in the differential diagnosis. (**Delicia Gentille-Lorente 1, Teresa Salvadó-Usach 2Sigmoid septum: A variant of the ventricular hypertrophy or of the hypertrophic cardiomyopathy? Arch Cardiol Mex. Apr-Jun 2016;86(2): 110-22. doi: 10.1016/j.acmx.2016.02.001**.)

Figure 1 Classical HOCM Septal asymmetrical variant with resting LVOTO and "S" shape or sigmoid septum (LV obstruction at subaortic level)



Scheme to assess the Wigle's score

This is a point score system, “the Wigle's score”, which takes into account the thickness of the ventricular septum, the presence of septal hypertrophy at papillary or apical levels, and the presence of anterolateral wall extension of hypertrophy; the score is the sum of these factors, spanning from 0 to 10. Figure 2



Scheme to assess the Wigle’s score, a point score system which takes into account the thickness of the ventricular septum (1= between 15 and 19 mm, 2= between 20 and 24 mm, 3= between 25 and 29 mm, and 4= ≥30 mm), the presence of septal hypertrophy at papillary (scored as 2) and/or apical (scored as 2) levels, and the presence of anterolateral wall extension of the hypertrophy (scored as

2). The total score is the sum of these individual factors and spans from 0 to 10. The magnitude and distribution of LVH, assessed by Wigle's score, is related to invasive indexes of passive diastolic dysfunction. HCM patients with severe LVH (Wigle's score ≥8) showed higher pulmonary capillary wedge pressure, LV end-diastolic pressure, and constant of chamber stiffness. (**Quirino Ciampi 1, et al. Effect of hypertrophy on left ventricular diastolic function in patients with hypertrophic cardiomyopathy. Heart Int. 2006;2(2):106. doi: 10.4081/hi.2006.106**.

III) Non-obstructive forms

- **Septal asymmetrical with reverse septal curvature with no obstruction**

Characterized by a septum hypertrophy as a reversed "S", more distant from the LVOT. This presentation does not cause obstruction to the LV outflow. The identification of this variant by CMR is characterized by a septal/free wall thickness ratio greater than 1.3 in the short-axis plane. (**Camici PG, Olivotto I, Rimoldi**

OE. The coronary circulation and blood flow in left ventricular hypertrophy. J Mol Cell Cardiol. 2012; 52:857-864.).

- **Variant with mid-ventricular obstruction with or without a LV apical diverticulum**

Characterized by a mid-ventricular hypertrophy that causes a local narrowing and, in severe cases, apical dilatation. In approximately 10% of patients, there may be apical aneurysm formation. (**Camici PG, Olivotto I, Rimoldi OE. The coronary circulation and blood flow in left ventricular hypertrophy. J Mol Cell Cardiol. 2012; 52:857-864**.). Apical aneurism is better diagnosed by CRM than echocardiography which, in turn, can fail to detect this change in 10% of cases. (**Argulian E, Chaudhry FA. Stress testing in patients with hypertrophic cardiomyopathy. Prog Cardiovasc Dis. 2012; 54:477-482**)

- **Apical Hypertrophic Cardiomyopathy or Yamaguchi syndrome**

(Ap-HCM): 2%, 3% to 8%; obliteration of LV cavity at the apex together with an apical wall thickness > 15 mm or a ratio between apical and basal LV wall thicknesses ≥1.3-1.5 cm[4]. This variant have a better prognosis than the other variants, although it

has been more associated with ischemia and apical myocardial infarction (***Wigle ED, et al.* Cardiomyopathy: The diagnosis of hypertrophic cardiomyopathy.*Heart. 2001 Dec; 86(6):709-14*.)**

- **Concentric, symmetrical, or homogeneous hypertrophic: 5%:**

It is characterized by diffuse parietal hypertrophy of LV with reduction of LV cavity. This variant may also be present in the so called, HCM phenocopies: amyloidosis, sarcoidosis and FD (**Noureldin AR, Liu S, Nacif MS, Judge DP, Halushka MK, Abraham TP, et al. The diagnosis of hypertrophic cardiomyopathy by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson.* 2012; 14:17–17**.) (**Hoey ET, Teoh JK, Das I, Ganeshan A, Simpson H, Watkin RW, et al. The emerging role of cardiovascular MRI for risk stratification in hypertrophic cardiomyopathy. *Clin Radiol.* 2014;69(3):221–230**.)

- **Focal HCM variant**

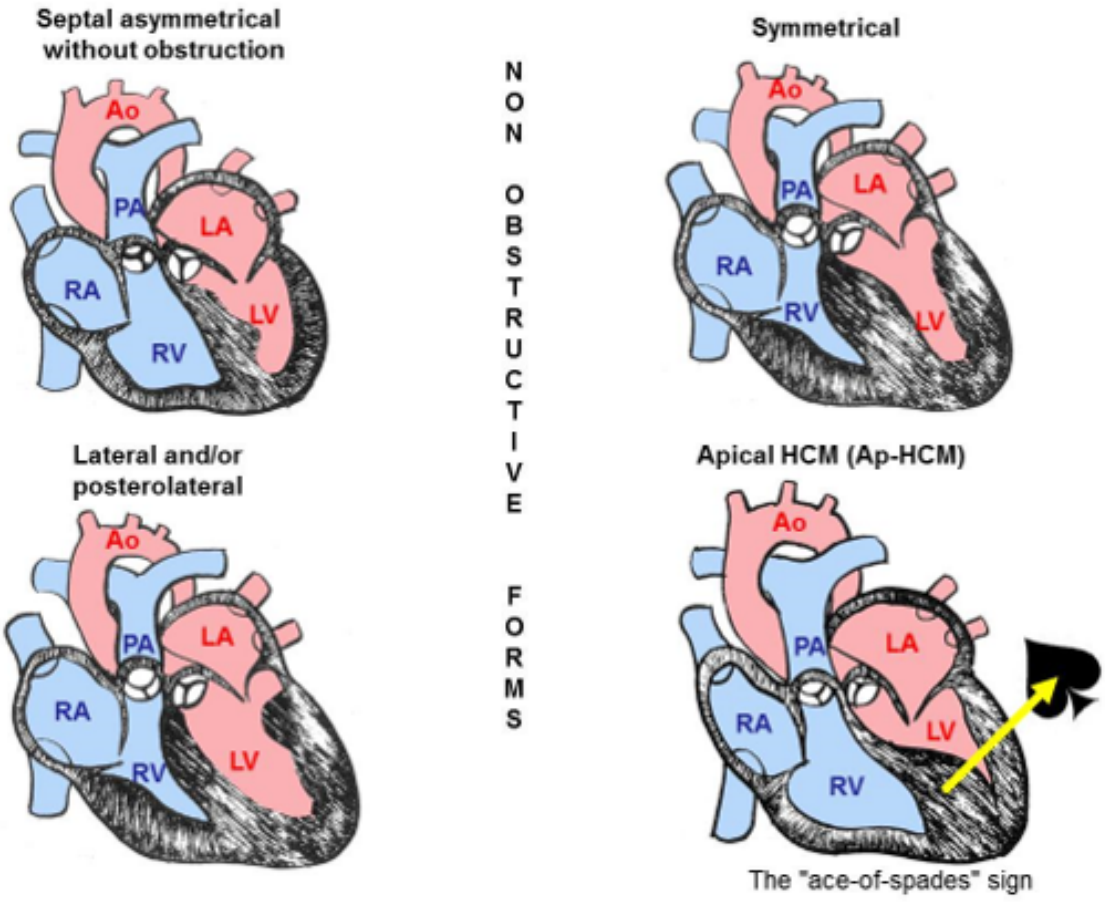
Characterized by hypertrophy located in the myocardium. CMR help distinguishing focal HCM from other cardiac masses, by identifying evidence of myocardial contractility in the former case. (**Camici PG, Olivotto I, Rimoldi OE. The coronary circulation and blood flow in left ventricular hypertrophy. J Mol Cell Cardiol. 2012; 52:857-864**.).

- **HCM in RV**

Occurs in 18% of HCM patients, generally involving the mid-and apical portion of the RV. This may cause RVOTO in severe cases. Increased maximum thickness of the RV wall (> 8 mm) has been shown by CMR in approximately 20% of HCM patients. **(Atteya G, Lampert R. Sudden Cardiac Death in Genetic Cardiomyopathies. Card Electrophysiol Clin. 2017; 9:581-603**.) Areas with increased wall thickness are commonly observed in the insertion of the RV wall into anterior and posterior septum, although the entire RV may be involved.

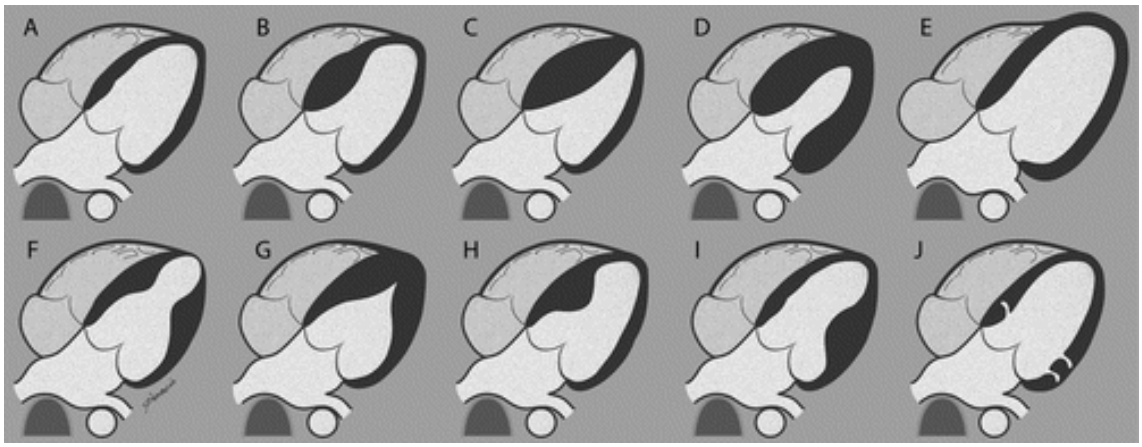
- Lateral and/or posterolateral HCM

Figure 3 Outline of Non-Obstructive forms of HCM



The exercise echocardiogram evidences latent obstruction easily induced by exercise in 60 to 75% of non-obstructive forms. The determination of the gradient under this condition must be considered in routine investigation of patients with mild or no obstruction at rest. The evaluation of HCM incorporates methods based on the ultrasound image, which, along with MRI, allow recognizing ventricular obstruction generating mechanisms, thus facilitating the diagnosis and management of obstructive and latent obstructive forms.

Figure 4 HCM phenotypes.



HCM phenotypes. Diagrams show normal or HCM-phenotype-negative cardiac morphology *(A)*, focal basal septum HCM*(B)*, diffuse septum HCM*(C)*, concentric and diffuse HCM*(D)*, burned-out phase HCM*(E)*, midventricular HCM*(F)*, apical HCM*(G)*, focal midseptum HCM*(H)*, free-wall HCM*(I)*, and crypts in genotype-positive and phenotype-negative HCM*(J)*.

Phenotypes of HCM

Asymmetrical HCM: Basal septal thickness ≥15 mm; ratio of septal thickness to thickness of inferior wall at midventricular level >1.5 The asymmetric septal form is the most common morphologic variant of HCM and accounts for up to 60%–70% of cases. In asymmetric HCM, the ventricular septum is disproportionately enlarged, with the anteroseptal myocardium

most commonly involved. The septal hypertrophy can be limited to the subaortic, midventricular, or apical regions. In some patients, the hypertrophy can be focal and may involve only one or two LV segments, most commonly involving the basal anterior septum, anterolateral free wall, posterior septum, and apex. At times, it may involve the entire length of the septum from base to apex or may extend and involve anterior or inferior walls of the LV. The normal thickness of the LV is 12 mm or less, measured during diastole. The diagnosis of asymmetric septal hypertrophy is made when septal thickness is greater than or equal to 15 mm or when the ratio of the septal thickness to the thickness of the inferior wall at the midventricular level is greater than 1.5.

Obstructive HCM: peak gradient at LVOT or mid LV cavity ≥30mm

Apical HCM Apical thickness ≥15 mm; ratio of apical LV wall thicknesses to basal LV wall thicknesses 1,3-1.5

Multiple clinical, genetic, and morphologic features, such as risk of SCD from arrhythmia, diastolic dysfunction, or LVOTO, the major determinant of progressive CHF. Consequently, HCM is a complex heart disease with variable hypertrophy location in the

LV and/or RV. Additionally, HCM is the most frequent monogenic cardiovascular entity, with most often AD inherited with variable expressivity and incomplete penetrance. (**Petryka J, Baksi AJ, Prasad SK, *et al.* Prevalence of inferobasal myocardial crypts among patients referred for cardiovascular magnetic resonance. Circ Cardiovasc Imaging. 2014; 7:259-264**.) HCMs are heterogeneous group of pathophysiological mechanisms and etiologies, which lead to the development of LVH, not explained by a significant and prolonged increase in post-load. OHCM is an inherited myocardial disease defined by cardiac hypertrophy (wall thickness ≥15 mm) that is not explained by abnormal loading conditions, and LVOT ≥30 mmHg, diastolic dysfunction, myocardial ischemia, and mitral regurgitation.