## Heart – Commissioned Editorial

## TITLE

### Evolution of Hypertrophic Cardiomyopathy in Sarcomere Mutation Carriers

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**Main Text**

Hypertrophic Cardiomyopathy (HCM) is, in most cases, caused by autosomal dominant mutations in sarcomere protein genes. How these mutations lead to the development of symptoms, heart failure and sudden death, via the familiar clinical phenotype including left ventricular hypertrophy (LVH) is beginning to be unravelled. Before overt LVH, there is an earlier, subclinical stage. The detection of this is also useful–in the US alone there are 600,000 or so people who either have subclinical HCM, or who have now passed into overt disease. In addition, there are a similarly important number of first-degree relatives in whom status may be uncertain. Considering a 'whole-of-life' approach to HCM, the ultimate goal would be to develop specific therapies that prevent disease onset (not just mitigate risk and symptoms), whilst at the same time robustly predicting who will and will not develop disease, and identify how to modify this. Understanding disease mechanisms and phenotype development is one likely route to these insights.

The subclinical phase of HCM occurs before overt LVH criteria are reached and it consists of a cluster of measurable abnormalities. Recognised electrocardiographic and imaging changes form the basis of the 1997 familial criteria,[1] where in spite of the relatively sparse data, minor and major criteria for its identification were constructed. Sparse data results in conflicting opinions however, with the later 2011 ACCF/AHA guidelines classifying a HCM sarcomere gene mutation carrier as "genotype-positive/**phenotype-negative**" leaving no room for a subclinical HCM state. Later guidelines (the 2014 ESC guidelines) acknowledged the subclinical phenotype but did not assign a firm status beyond "*The clinical significance of mild morphological and functional abnormalities is uncertain...*".

Since the familial criteria almost 20 years ago, there has been progress in understanding phenotype development with additional identified changes, particularly noticeable when complementary imaging techniques are combined (e.g., echocardiography and cardiovascular magnetic resonance [CMR]). This combined imaging approach permits the identification of at least 8 morpho-functional changes in subclinical HCM (**Table 1**). Reviewing these changes, some look suspiciously embryological in origin (crypts, abnormal trabeculation) whereas others (mitral valve leaflets) could be acquired or embryological. Phenotype evolution in HCM may therefore be the result of two overlapping processes–measureable phenotype changes that happen on the pathway towards overt LVH overlaid on top of changes that may arise since the earliest expression of sarcomere protein genes in utero during cardiac embryogenesis.

To understand these changes, we will therefore need to change our mind-set and exploit a portfolio of scientific approaches: 1) preclinical studies investigating the cardiac embryonic morphology of small animal models of HCM; 2) pathological information from the necropsy of non-hypertrophied hearts of HCM sarcomere gene mutation carriers affected by sudden cardiac death (SCD); 3) observational clinical studies exploring the imaging phenotype of subclinical HCM (predominantly echo and CMR-based); and importantly, 4) longitudinal clinical studies investigating outcomes and phenotype progression in subclinical HCM, like the one reported in this issue of *Heart*, by Ho et al.

Preliminary such approaches are starting. Looking at cardiac development, in heterozygous myosin-binding protein C (*Mybpc3*)-targeted knock-out mice,[2] an increased number of myocardial crypts compared to wild-type are present, together with an altered trajectory of trabecular changes and an exaggeration of otherwise subtle asymmetric septal hypertrophy. These confirm that at least some aspects of the subclinical HCM phenotype can establish themselves during cardiac embryogenesis and future work should focus on elucidating the underlying mechanisms. If HCM sarcomere gene mutations in humans have a similar ability to alter the cardiac developmental trajectory, new avenues for early and specific pharmacological therapies become potentially available, but will need to be started early.

Post-mortem studies of subclinical HCM are rare. In one such study, the hearts of 4 related SCD victims that appeared macroscopically normal in terms of mass and wall thickness, demonstrated widespread myocardial disarray[3] and a pathogenic HCM-causing troponin T (*TNNT2*) mutation was later implicated. In a more recent UK regional post-mortem registry, 9 hearts from athletes with SCD who again showed normal wall thickness and mass, had microscopic features consistent with HCM.[4] Collectively these data suggest that the subclinical HCM state (before the development of LVH) may on occasions not be entirely benign.

In the present work[5]−the first prospective multi-modality [echo and CMR] imaging study of subclinical HCM−Ho et al. followed up 38 HCM sarcomere gene mutation carriers (58% female) free of LVH for a median of 2.9 years, to elucidate factors contributing to HCM phenotype progression. The 4 carriers who went on to develop LVH carried more highly penetrant mutations (either β-myosin heavy chain [*MYH7*] or TNNT2), had higher LV ejection fraction, evidence of diastolic dysfunction, higher N-terminal pro-brain natriuretic peptide levels, longer posterior mitral leaflets, and more electrocardiographic abnormalities.

In an earlier study, Pasquale et al. reported longer outcome data on a total of 24 *TNNT2* carriers (11 adults and 13 children) all with normal echo at baseline. Adults and children were followed up for 8.7 ± 5.2 and 6.7 ± 3 years respectively, and a total of cases 4 progressed to LVH.[6] One carrier with a subclinical HCM phenotype (maximal wall thickness 9 mm by echo) died suddenly.[6] In the process of developing the refined risk prediction model for SCD in HCM, Mohoney et al. again discovered how 22 HCM patients (4% of 546) experienced SCD in spite of a maximal wall thickness ≤14 mm.[7]

Whilst these studies are important, what is needed now is a scaling up. We have the tools–genotyping facilities, high-sensitivity assays for serum biomarkers and CMR and echocardiographic imaging expertise are now co-localised and available in many tertiary centres so we are in a stronger position to answer key questions about the wider HCM disease spectrum and development. We can start to answer questions about whether all HCM patients exhibit a subclinical phenotype and whether it differs by gene (and/or amino acid) mutation? One study (see **Table 1**) shows that *MYBPC3* mutation carriers may have a 2-fold increased prevalence of crypts and less LV systolic cavity reduction compared with the other combined mutations, but large scale cohort data is needed to understand generalizability of findings. What is the precise role of serum biomarkers reflecting LV wall stress, in the risk stratification of patients with subclinical HCM? Finally, what about those subjects without a recognised mutation and what if any, is the synergistic impact of gender, afterload, levels of physical activity, and endocrine/social factors on HCM phenotype evolution?

In HCM patients, typical practice is to perform target resequencing analysis of a predefined panel of at least 8 commonly implicated sarcomere protein genes using next-generation sequencing. If a pathogenic disease-causing variant is found in the index case, cascade genetic screening of family members may help identify those at risk of developing HCM. Once a HCM-causing mutation is identified, current data on genotype-phenotype correlations have been disappointing for their abilities to effectively change management. This may be because we may have been searching for correlations too late in the course of the disease−the vast majority of genotype-phenotype correlation studies, save a few paediatric studies,[6] were on patients already expressing overt disease and herein, we believe, lies the problem: once LVH manifests, all HCM appears to converge and look similar (within a progression spectrum) with hypertrophy, fibrosis and disarray and a final common phenotype−potentially, early phenotype diversity may transition to phenotype convergence over time.

We, like Ho et al. are of the belief that large-scale research efforts focusing on the systematic, high-resolution and multi-modality scrutiny of the ***early*** (subclinical) HCM phenotype, may offer superior genotype-phenotype insights into prognosis and response to therapy. In this regard, we point out how the highly anticipated LIBERTY-HCM study (Impact of Late Sodium Current Inhibition on Exercise Capacity in Subjects with Symptomatic Hypertrophic Cardiomyopathy) is due to investigate the role of the late sodium current inhibitor eleclazine on exercise capacity and related symptoms in HCM, but will not be recruiting participants with subclinical HCM.[8] It may be that if we can define subclinical HCM better, early therapy may have success. Other imaging studies are similarly focusing on established disease such as the large 44-site, 2,750-patient international prospective HCM registry that will only be studying overt HCM (wall thickness ≥15 mm)[9].

In spite of genetic testing, no causative HCM mutation is found in about 30% of index cases and management of these patients and their family members remains an unmet clinical need. We do not, at this stage, know about subclinical disease in these subjects. Multimodality imaging and whole exome sequencing may prove helpful perhaps by exploiting a more sophisticated approach comparing data layers according to a probabilistic classification of variants ("pathogenic", "likely pathogenic", "variants of uncertain significance", "likely benign", "benign") and taking into account any potential modulatory effect of gender (or other potential influential factors) on HCM phenotype expression. We are only just starting to understand the

subclinical HCM phenotype. The study by Ho et al. points the way ahead and one that may just unlock those elusive genotype-phenotype correlations in HCM that may ultimately prove useful in altering patient care.

**References**


1 McKenna WJ, Spirito P, Desnos M, *et al.* Experience from clinical genetics in hypertrophic cardiomyopathy: proposal for new diagnostic criteria in adult members of affected families. *Heart* 1997;**77**:130–2.

2 Captur G, Ho CY, Schlossarek S, *et al.* The embryological basis of subclinical hypertrophic cardiomyopathy. *Sientific Reports* 2016;**8**:1–10.

3 McKenna WJ, Stewart JT, Nihoyannopoulos P, *et al.* Hypertrophic cardiomyopathy without hypertrophy: two families with myocardial disarray in the absence of increased myocardial mass. *Br Heart J* 1990;**63**:287–90.

4 Finocchiaro G, Papadakis M, Robertus J-L, *et al.* Etiology of Sudden Death in Sports: Insights From a United Kingdom Regional Registry. *J Am Coll Cardiol* 2016;**67**:2108–15.

5 Ho CY, Cirino AL, Lakdawala NK, *et al.* Evolution of hypertrophic cardiomyopathy in sarcomere mutation carriers. *Heart* 2016;:1–10.

6 Pasquale F, Syrris P, Kaski JP, *et al.* Long-term outcomes in hypertrophic cardiomyopathy caused by mutations in the cardiac troponin T gene. *Circ Cardiovasc Genet* 2012;**5**:10–7.

7 O'Mahony C, Jichi F, Pavlou M, *et al.* A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J* 2014;**35**:2010–20.

8 Olivotto I, Hellawell JL, Farzaneh-Far R, *et al.* Novel approach targeting the complex pathophysiology of hypertrophic cardiomyopathy- the impact of late sodium current inhibition on exercise capacity in subjects with symptomatic hypertrophic cardiomyopathy (LIBERTY-HCM) trial. *Circ Hear Fail* 2016;**9**:e002764.

9 Kramer CM, Appelbaum E, Desai MY, *et al.* Hypertrophic Cardiomyopathy Registry: The rationale and design of an international, observational study of hypertrophic cardiomyopathy. *Am Heart J* 2015;**170**:223–30.

**TABLE**

**Table 1. The cluster of morpho-structural abnormalities identifiable in patients with subclinical HCM.**

| Feature* | [Modality] How to measure | Cut-off | Main References§ |
|---|---|---|---|
| **AMVL elongation** | [CMR] 3-chamber cine view in diastole with leaflet maximally extended parallel to the anterior septum and LV free wall. | 21 ± 3 mm | Maron et al. Circ 2010. |
| **PMVL elongation** | [CMR] As above | 11 ± 2 mm | Maron et al. Circ 2010. |
| **Myocardial crypts** | [CMR] 2- or 4-chamber long axis cine image in end-diastole as narrow and deep blood-filled invaginations contiguous with the LV cavity adjacent to normal-appearing myocardium, and not visible at end-systole. | ≥50% of adjacent WT | Maron et al. Circ Imaging 2012. |
| **Abnormal diastolic function^** | [TTE] Reduced early diastolic annular velocity detected by tissue Doppler imaging (speckle-tracking) of the mitral annulus. | 10.2 ± 2.5 cm/s | Kauer et al. Echocardiography 2012. |
| **High ECV** | [CMR] Look-Locker sequence applied to 3 parallel LV short axis slices (basal, mid, apical) and 16-segment analysis as previously reported. | 0.33 ± 0.01 | Ho et al. Circ Imaging 2013. |
| **Abnormal trabeculae** | [CMR] Box-counting fractal analysis applied to cine LV stack. | 1.249 ± 0.07 | Captur et al. Circ Gen 2014. |
| **Reduced LVESV$i_R$** | [CMR] LV ESV calculated using standard volume analysis software from the LV cine stack. The gender and age specific variable LVESV$i_R$ is computed as a ratio of the measured BSA-indexed LVESV ($_{measured}$LVESV$i$, ml/m$^2$) divided by the expected BSA-indexed LVESV ($_{expected}$LVESV$i$, ml/m$^2$) in the published literature. | < 0.803 | Captur et al. Circ Imaging 2014.‖ |
| **Abnormal septal convexity** | [CMR] 4-chamber cine view in end-diastole taking the maximal distance between the LV endocardial border reference line and the intersection point perpendicularly to a reference line joining at mid-wall the level of tricuspid valve insertion and the apical right ventricular insertion point into the LV. | 5.0 ± 2.5 mm | Reant et al. JCMR 2015. |

* Ordered by year of publication.

§ Reference list is non-exhaustive - other references may exist that are not necessarily listed here.

^ Discrepancies in the echocardiographic literature exist potentially caused by angle-dependence of tissue Doppler imaging.

‖ This study showed that myosin-binding protein C sarcomere gene mutation carriers may have a higher prevalence of crypts and less LV systolic cavity reduction compared with the other combined mutations.

AMVL, anterior mitral valve leaflet; CMR, cardiovascular magnetic resonance; ECV, extracellular volume; LV, left ventricle; LVESV$i_R$, normalized body surface area-indexed left ventricular end-systolic volume; PMVL, posterior mitral valve leaflet; TTE, transthoracic echocardiography; WT, wall thickness.