Diagnosis of hypertrophic cardiomyopathy in an athlete: tricks and pitfalls

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Sudden Death in Young Athletes

FIGURE 1. Diagram summarizing the cause of death in 29 competitive athletes. CV = cardiovascular; LVH = left ventricular hypertrophy.

*Includes one patient who also had anomalous origin of the left coronary artery from the anterior sinus of Valsalva. The hearts of four other patients in this subgroup were initially referred for evaluation because of suspected cardiac disease; subsequently, these patients were identified as having been competitive athletes during life.
HCM is defined by unexplained LV hypertrophy associated with non-dilated ventricular chambers in the absence of a cardiac or systemic disease that itself would justify the magnitude of hypertrophy evident...

Clinically, HCM is recognized by a maximal LV wall thickness ≥13 mm. However, any degree of wall thickness is compatible with the diagnosis of HCM in the presence of genetic substrate...

About 2-4% of athletes show LV wall thickening which rises the differential diagnosis with HCM.
Athlete’s Heart or HCM?

LVWT 13 mm

LVWT 13 mm
How can we reach the diagnosis?

Assess the utility (availability vs. diagnostic power) of the current diagnostic techniques to distinguish HCM from the athlete’s heart.
Imaging techniques in the HCM diagnosis

what to look for:

1. Shape of LV cavity
2. Dimension of LV cavity
3. Asymmetry of LV wall thickening
4. Maximum LV wall thickening
5. LGE
6. Accessory morphologic abnormalities (mitral valve elongation, abnormal papillary muscle, crypts)
What to look for in HCM patients

1. Abnormal shape of LV cavity
2. Normal (or mildly reduced) dimension of LV cavity ($\leq 54$ mm?)
Global Left Ventricular Shape Is Not Altered as a Consequence of Physiologic Remodeling in Highly Trained Athletes

Antonio Pelliccia, MD, Erick Avelar, MD, Stefano De Castro, MD, and Natesa Pandian

Highly trained athletes present increased left ventricular (LV) cavity dimension, wall thickness, and mass, which are regarded as physiologic adaptations to intensive athletic conditioning. In elite athletes, LV cavity dimension and wall thickness may increase substantially, raising the dilemma of distinguishing these extreme morphologic expressions of "athlete’s heart" from structural cardiac diseases, such as hypertrophic or dilated cardiomyopathy. Although a group of 14 untrained controls was recruited from the administrative personnel of the Italian National Olympic Committee. They were matched for age, gender, and ethnic origin. Body surface area was mildly smaller than in athletes (1.98 ± 0.14 vs 2.13 ± 0.14 m², respectively; p <0.005); no control was involved in a regular athletic activity, but 6 occasionally played soccer. All subjects included in this study were judged to be free from cardiac disease on the (Am J Cardiol 2000; 86: 700-702)
What to look for in HCM patients

3. Asymmetric/segmental LV wall thickening
4. Maximum wall thickening (>15 mm ?)
What to look for in HCM patients

5. LGE

The presence of LGE within the localized area of LV hypertrophy supports the diagnosis of HCM.

Presence of LGE (>15% of LV mass) is associated with incidence of VAs and represents an independent risk for SCD.
What to look for in HCM patients

6. Accessory morphologic abnormalities (mitral valve elongation, abnormal papillary m. insertion, crypts)
What is of little help in diagnosis of HCM in trained athlete:

- LA enlargement
- Diastolic dysfunction
- Exercise performance

Elite marathon runner with apical HCM and enlarged LA (44 mm)
Strain is a measure of deformation of myocardial wall.

Strain rate is the velocity of deformation of myocardial wall.

\[
\text{Strain(\%), } \varepsilon = \frac{(L_0 - L_1)}{L_0}
\]

\[
\text{Strain rate } = \frac{\varepsilon}{\text{sec}}
\]
Circumferential, transverse and longitudinal strain significantly reduced in HCM patients compared to athletes and controls. Longitudinal strain reduced more in hypertrophied segments.
Echocardiography or CMR?

- Diagnostic images usually achievable
- Large availability, and reproducibility
- Low cost
- High spatial resolution images
- Tomographic reconstruction of heart
- LGE

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Suspected athletes with abnormal ECG
- Echo: 100%
- CMR: 24%
- Other testing: +15%
- Identified with CMPs: 44%
Relevance of gene analysis for HCM

(courtesy, Maron BJ and Maron S)
Two decades of intensive investigations have defined the HCM genetic background. At present we know 11 causative gene anomalies, with over 1400 mutations identified...
Gene testing in screening athletes for HCM?

- **Yield for positive gene testing in probands is 50%, and likely <25% in individuals outside family screening.**

- **VUS** (Variants of uncertain clinical significance)

- **G+P-** (Genotype positive, phenotype negative individuals)
Criteria used to evaluate pathogenicity of HCM mutation

Assessment of the pathogenic status to an HCM mutation is made on probabilistic basis, and not as binary result (yes or not)

- Cosegregation: whether mutation is present in patients with LVH
- Prior evidence: if mutation was disease-causing in previous patients
- Controls: if mutation is absent in large, healthy population cohort
- Major disruption in protein structure, judged to alter functional properties
Clinical significance of HCM mutations

The reduced cost of technology nowadays allows DNA sequencing of the whole genome, increasing recognition of VUS (in up to 50% of the tests).
**Genotype +, Phenotype -**

$G^+ P^-$ represents an expanding subset of genetically affected individuals without evidence for LVH. However, they may have:

1. increase collagen synthesis, and abnormal proportion of interstitial fibrosis (pro-arrhythmogenic substrate);
2. impaired LV relaxation properties;
3. energy metabolism impairment;

**Open questions:**
1. are these individuals at risk for SCD?
2. Can exercise and sport participation triggers/worsen development of LVH?
3. Any prophylactic treatment advised?
The introduction about 25 years ago of gene analysis in HCM was associated with substantial optimism and great expectation ...

HCM genotyping is a very complex process. The novel techniques for generating genetic data (next generation sequencing) will further increase the complexity of the process. Paradoxically, the gap is increasing in translating the genetic information to clinical decisions, making genetic analysis less useful in the clinical practice.
A “novel” technique in the diagnosis of the HCM

The 12-lead ECG
ECG abnormalities precede LVH in HCM

Risk of sudden death increases with phenotypic expression
12-lead ECG abnormalities in HCM

- Diffuse T-wave inversion in antero-lateral (V$_{4-6}$) and inferior (II,III,VF) leads, often with ST-Segment depression (60%)
- Pathologic Q-waves (30%)
- Left atrial enlargement (25%)
- Conduction abnormalities (25%)
- Left axis deviation (5%)
- Isolated increase in R/S voltages (5%)
- Normal Patterns (5%)
MM, soccer player at age of 28 years
Same athlete, at the age of 33 years
Long-term follow-up of athletes with abnormal ECG

Study group 81

9-year follow-up

No symptoms, no CV disease 70

CV disease (hpt3, CAD 1, myoc 1, SVT 1) 6

CMPs (HCM3; ARVC1; DCM1) 5

1, sudden death
1, cardiac arrest
12-lead ECG abnormalities in HCM

Pathologic Q-waves (up to 30%)

Left atrial enlargement (up to 25%)
Proposal for revised (2016) Seattle criteria

**Training related normal findings**
- Sinus bradycardia
- First degree AV block
- Incomplete RBBB
- Early repolarisation
- Isolated QRS voltage criteria for LVH

**Borderline (minor abnormal) findings**
- Left Atrial enlargement
- Right atrial enlargement
- Left axis deviation
- Right axis deviation
- Right ventricular hypertrophy
- T-wave inversion in leads V1-V4 in Black athletes

**Training unrelated abnormal findings**
- ST segment depression
- Pathological Q waves
- T-wave inversions beyond V1 in Caucasian athletes; beyond V4 in Black athletes
- Complete LBBB or RBBB
- QTc $\geq$ 470ms
- Brugada like pattern
- Atrial or ventricular arrhythmias
- $\geq$ 2 PVCs per 10 sec

If found in isolation considered normal

If 2 or more patterns present considered abnormal
Echocardiography remains the first-step imaging modality in the athlete. Be aware of the possible pitfalls (missing segmental LVH).

CMR is the best imaging modality for diagnosis, with recognition of segmental LVH and presence of LGE. Mandatory in all controversial cases.

Gene test complex is in HCM, with increasing number of VUS. Often difficult to translate genetic information into clinical practice.

ECG is abnormal in over 90% of HCM patients, even before LVH. Needs appropriate interpretation.
Thank you for your attention

See also: www.antoniopelliccia.it
Outcome in Genotype + Phenotype - HCM

66 individuals from families with known HCM mutations

- n= 23 G- P- (normals)
  - No HCM

- n= 12 G+ P- (carriers)
  - 2 HCM

- n= 24 G ? P – (unknown)
  - No HCM

12-year follow-up

No CV events and no symptoms
CMR allows complete tomographic reconstruction of the whole heart.
Maron and Pelliccia, since 1995

“Gray-zone” of LVH
(males: 13-15 mm)
(females: 11-13 mm)

Asymmetric pattern of LVH
(< 45 mm) LV cavity (> 54 mm)

Abnormal LV filling & relaxation
(with nondilated LV)

Left atrium↑ (with enlarged LV)

↓ thickness with deconditioning

Pathogenic sarcomeric mutations

CMR delayed g. enhancement ?

Exercise performance (VO2 max>120%) ?
Left atrium in Athlete’s Heart vs. HCM

(42 ± 4 mm)  p<0.001  (34 ± 5 mm)
LV filling/relaxation in AH vs. HCM
Myocardial strain in athlete’s heart vs. HCM
Infero-lateral T-wave Inversions in Black vs. White Athletes

(from Sharma et al., 2012)
Utility of echocardiography, PW Doppler, TDI

- 25 HCM patients (TUFTs, Boston, MA)
  - "Gray-zone" 13-15 mm
  - All males of same age and BSA

- 28 elite athletes (ISM, Rome, Italy)
## Sensitivity and specificity for diagnosis of HCM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cutoff</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV End-diastolic diameter (mm)</td>
<td>&lt;54</td>
<td>100</td>
<td>100</td>
<td>&lt;0.001</td>
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<tr>
<td>Left atrium</td>
<td>&lt;0.40</td>
<td>92</td>
<td>71</td>
<td>&lt;0.001</td>
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<td>TDI e' (cm/s)</td>
<td>&lt;11.5</td>
<td>83</td>
<td>61</td>
<td>&lt;0.001</td>
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<td>Doppler A-wave</td>
<td>&gt;46</td>
<td>60</td>
<td>74</td>
<td>0.003</td>
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