LVH
GREY ZONE OF HYPERTROPHIED VENTRICLES

Unit of Inherited and Rare Cardiac Diseases
Heart Center for the Young and Athletes
Onassis Cardiac Surgery Centre
Common phenotype different causes

Diagnosis of LVH  a starting point

By Jacopo Olivotto
Causes of Left Ventricular Hypertrophy

Diagnosis of LVH is a starting point

- Genetic
  - Friedreich’s Ataxia
  - Noonan Syndrome
  - LEOPARD syndrome

- Physiological
  - ACE
  - Racial
  - Gender

- Metabolic
  - Mitochondrial disease
  - Fatty Acid Metabolism
  - Fabry’s disease
  - Glycogen storage

- Amyloid
- Infants diabetic mothers
- Phaeochromocytoma

Hypertension
Athletes
SUBCLINICAL FORM OF HCM DUE TO EVOLUTION
Mutation: Arg286Cys

CONCEALED FORM OF HCM DUE TO SUBCLINICAL EXPRESSION
Apart from channelopathies, subclinical forms of inherited structural heart diseases would appear to be implicated in SADS.
Left Ventricular Wall Thickness in 911 Adult Male Black athletes and 858 Adult Male White Athletes

Maximal LVWT %

13% 2%
Athletes heart vs HCM

Am J Cardiol 2014

Athlete:
End diastolic diameter = 58 mm
Wall thickness = 13 mm

HC patient:
End diastolic diameter = 48 mm
Wall thickness = 13 mm
ECHO

Strenth athlete

LVWmax: 12-13
LVEDD: 48 mm
## Differential Diagnosis  
HCM vs Athletic Heart Syndrome*

*Athletes with LVH in Grey zone*

### A. Stage A
- Clinical examination
  - History
  - Family history
  - Physical examination
- ECG
- ECHO – Doppler – TDI
- Blood and urine tests

### B. Stage B
- Holter rhythm
- Cardiopulmonary exercise testing
- Exercise ECHO
- **Clinical evaluation of the family** (Stage A or B?)
- Cardiac MRI – LGE

### C. Stage C
- **Detraining?**
- Genetics
Υπερτροφική μυοκαρδιοπάθεια

= Φυσιολογικό άτομο

= Υπερτροφική μυοκαρδιοπάθεια

= Φυσιολογικό άτομο
MRI
WEIGHT OF EVIDENCE?

LVH: 12mm
LVEDD: 47 mm
ECG: mild repolarization changes
MRI: significant LGE

HOLTER: NSVT

CAUSETIVE MUTATION on MHY7
Cardiomyopathy/LV Hypertrophy in Athletes

Gray-zone of LV hypertrophy

Hypertrophic Cardiomyopathy

Wall thickness 13-15 mm

Athlete’s Heart

LV cavity

≥55 mm

<55 mm

<40 mm

Left atrium

≥40 mm

Abnormal

LV filling/relaxation

Normal

Present

Diffusely inverted T-wave

Absent

Positive

Family History

Negative
MULTI FACTORIAL APPROACH

FACTORS
- DEMOGRAPHICS
- ECG
- STRUCTURAL CHARACTERISTICS
- FUNCTIONAL CHARACTERISTICS
- LAB TEST
- OTHERS

Family history of HCM
Female gender

“Gray Zone” of LV Wall Thickness (13-15 mm)

HCM
Athlete’s Heart

Unusual patterns of LV hypertrophy
LV cavity < 45mm
LV cavity > 55mm
Left atrial enlargement
Bizarre ECG patterns
Abnormal LV filling
Female gender
Thickness with deconditioning
Family history of HCM
Max. VO₂ > 45 ml/kg/min > 110% predicted
CMR—gadolinium delayed enhancement
Clinical features that assist in the differential diagnosis of hypertensive heart disease and hypertrophic cardiomyopathy

<table>
<thead>
<tr>
<th>Clinical features favouring hypertension only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal 12 lead ECG or isolated increased voltage without repolarisation abnormality</td>
</tr>
<tr>
<td>Regression of LVH (LV mass or voltage LVH) over 6–12 months of aggressive antihypertensive treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical features favouring hypertrophic cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of HCM</td>
</tr>
<tr>
<td>Right ventricular hypertrophy</td>
</tr>
<tr>
<td>Late gadolinium hyperenhancement at the RV insertion points or localized to segments of maximum LV thickening on CMR</td>
</tr>
<tr>
<td>Maximum LV wall thickness ≥15 mm (Caucasian); ≥20 mm (black)</td>
</tr>
<tr>
<td>Severe diastolic dysfunction</td>
</tr>
<tr>
<td>Marked repolarisation abnormalities, conduction disease or Q-waves on 12 lead ECG</td>
</tr>
</tbody>
</table>
Gray-zone of LV hypertrophy

HPT athlete

Wall thickness
13-15 mm

Athlete’s Heart

LA ml/m²

C/P EXERCISE
peakVO₂>120%pred

NO

YES

FEMALES

NO

ECG INVERTED T waves

IMPAIRED
HR reserve

NO

YES

30+-5

26+-5

Abnormal

LV filling/relaxation

Normal

Present

Absent
Clinical evaluation
- Pedigree
- Signs
- Symptoms
- ECG
- Echo
- CMR
- Laboratory

Diagnostic red flags
- Features suggesting a specific disease?
  - yes
    - Further specialised tests & multidisciplinary input
    - Specific genetic/acquired disorder
  - no
    - Genetic testing

Genetic Testing
- Genetic testing
  - Definite disease causing sarcomere protein gene mutation
  - No definite disease causing sarcomere protein identified

ESC
HCM GUIDELINES
2014
Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases

Claudio Rapezzi, Eloisa Arbustini, Alida L. P. Cavorio, Philippe Charron, Juan Gimeno-Blanes, Tiina Heliö, Ales Linhart, Jens Mogensen, Yigal Pinto, Arsen Ristic, Hubert Seggewiss, Gianfranco Sinagra, Luigi Tavazzi, and Perry M. Elliott*
DIAGNOSTIC WORK UP IN CARDIOMYOPATHIES

First level

CK
Renal function
Proteinuria
Liver function tests

RAPEZZI ET AL EUR HEART J 2012

DANON or MITOCHONDRIAL
FABRY or MITOCHONDRIAL
FABRY or MITOCHONDRIAL
AMYLOIDOSIS
DANON or MITOCHONDRIAL
MEDICAL HISTORY:

✓ PAF - AMIO (IV) - SR
✓ DEEP VENOUS THROMBOSIS 3 y ago (sintrom),
✓ PALPITATION (often).
✓ HEAT INTOLERANCE

FAMILY HISTORY (-)

MALE 33 y old
Persistent AF
MILD LEFT VENTRICULAR HYPERTROPHY
CLINICAL CARDIAC EXAMINATION

S1-S2  NORMAL HEART SOUNDS

NYHA II

SYSTOLIC MURMUR 2/6

BP:100/80mmHg

LEG LYMPHOEDEMA..
<table>
<thead>
<tr>
<th>Peak Cardiovascular Responses</th>
<th>Predicted</th>
<th>Measured</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2 (ml/kg/min)</td>
<td>38.8</td>
<td>17.7</td>
<td>46</td>
</tr>
<tr>
<td>VO2 (l/min)</td>
<td>2.717</td>
<td>1.238</td>
<td>46</td>
</tr>
<tr>
<td>VCO2 (l/min)</td>
<td></td>
<td>1.158</td>
<td></td>
</tr>
<tr>
<td>Work (Watts)</td>
<td>224</td>
<td>96</td>
<td>43</td>
</tr>
<tr>
<td>Anaerobic Threshold (AT)(l/min)</td>
<td>&gt; 1.087</td>
<td>0.501</td>
<td></td>
</tr>
<tr>
<td>AT (% Predicted Max VO2)</td>
<td>&gt; 40%</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>188</td>
<td>105</td>
<td>56</td>
</tr>
<tr>
<td>O2 Pulse (ml/beat)</td>
<td>14.5</td>
<td>11.8</td>
<td>82</td>
</tr>
<tr>
<td>Systolic Blood Pressure (Max)</td>
<td>185</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic Blood Pressure (Max)</td>
<td>85-105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate Reserve (bpm)</td>
<td>&lt;15</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Peak Ventilatory Responses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VE Max (l/min) BTPS</td>
<td>98.0</td>
<td>44.6</td>
<td>45</td>
</tr>
<tr>
<td>Tidal Volume (VT) (L)</td>
<td>2.319</td>
<td>1.082</td>
<td>47</td>
</tr>
<tr>
<td>Respiratory Rate (RR)</td>
<td>&lt;50</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Breathing Reserve (%)</td>
<td>20-40</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Gas-Exchange Responses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End Tidal CO2 (Peak PetCO2)</td>
<td></td>
<td>42.4</td>
<td></td>
</tr>
<tr>
<td>End Tidal O2 (Peak PetO2)</td>
<td></td>
<td>104.7</td>
<td></td>
</tr>
<tr>
<td>VE/VO2 @ AT</td>
<td></td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>VE/VCO2 @ AT</td>
<td></td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>VE/VT (Est) @ Rest</td>
<td>0.30</td>
<td>0.27</td>
<td>91</td>
</tr>
<tr>
<td>VE/VT (Est) Peak</td>
<td>0.18</td>
<td>0.25</td>
<td>140</td>
</tr>
<tr>
<td>Respiratory Quotient (RQ)(Peak)</td>
<td>1.1-1.3</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>SpO2 (O2 Sat--Pulse Ox) @ Peak</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MRI

- LV normal dimension and function
- LVWmax 12mm
- RV within normal limits
- MR mild to moderate.
- **MILD LGE (+).**
MILD HCM?
HCM ?

angiokeratoma

LYMPHOEDEMA
So far....

- MILD LEFT VENTRICULAR CONCENTRIC HYPERTROPHY
- EF: 60%
- ABNORMAL ECG – AV conduction defect
- NYHA II-III (VO2max 49%)
- History of PAF
- LGE – mild
- ANGIokeratoma
- LEG LYMPHOEDEMA
- NO FAMILY HISTORY

What is next
Reconsider the patient

Pedigree
- Autosomal dominant
- Autosomal recessive
- X-linked-Dystrophin, Danon.
- Maternal

Symptoms
- Deafness (AFD, Epicardin)
- Muscle pains/weakness (Dystrophin)
- Paraesthesia
- Muscle weakness
- Postural hypotension
- Rash (lentigenes, angiokeratomata)

Physical exam
- Premature conduction disease
- Pseudo-infarct pattern

ECG
- Creatinine kinase (dystrophic, Danon, Desmin)
- Serum creatinine
- Proteinuria
- Ferritin
- Lactate

Laboratory
- Pattern of hypertrophy
- Valve disease
- Pericardial effusion
- Pattern of gadolinium hyperenhancement

Echo/MRI
- Exercise test: premature acidosis
- Endomyocardial biopsy

Other
- Genetics
HCM- FABRY DISEASE

Angiokeratoma

Preexcitation

Lab Test
Proteinuria
A Galactosidase

Inheritance
Genetics

Concentric Mild LVH

Lymphoedema
# GENETIC ANALYSIS

<table>
<thead>
<tr>
<th>GENE</th>
<th>VARIANT</th>
<th>RESULT</th>
<th>PATHOGENICITY</th>
<th>No of Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLA</td>
<td>NP_000160.1:p.Pro259Leu</td>
<td>Heterozygosis</td>
<td>Pathogenic or disease-causing mutation</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>NM_000169.2:c.776C&gt;T</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NC_000023.10:g.100653798G&gt;A</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Genetic Analysis Diagram]
TREATMENT

- Sotalol 80 1x2
- Triatec 2.5 1x1
- Sintrom 4 mg

- ERT
RCM

CK;
Renal function; Proteinuria
Liver function tests
Haemoglobin and white blood cell count
Serum iron, Ferritin
Urine and plasma protein immunofixation, free light chains

RAPEZZI ET AL
EUR HEART J 2012
ID: 013052015
13-May-2015 11:35:54

Sex: Male
Caucasian
Height: 179 cm
Weight: 76 kg

Vital Signs:
- Heart Rate: 57 bpm
- PR Interval: 206 ms
- QRS Duration: 132 ms
- QTc: 426 ms
- R-R Axes: 35° 255° 18°
- BP: 125/70 mmHg

Diagnoses:
- Sinus bradycardia with premature atrial complexes
- Right bundle branch block
- Inferior infarct, age undetermined
- Abnormal ECG

Technician:
Test Ind:

Referred by:
Unconfirmed
**FINDINGS**

- Creatine kinase
- Proteinuria with/without↓glomerular filtration rate
- Transaminase
- High transferrin saturation/ hyperferritinaemia
- Lactic acidosis
- Myoglobinuria
- Leucocytopenia

**RCM**

- Desminopathies
- Amyloidosis
- Haemochromatosis

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**RAPEZZI ET AL EUR HEARTJ 2012**
### Recommended laboratory tests in adult patients with hypertrophic cardiomyopathy

#### Brain natriuretic peptide and troponin T

- Elevated plasma levels of BNP, NT-proBNP and troponin T are associated with higher risk of cardiovascular events, heart failure and death.

#### AMYLOIDOSIS DANON
Recommended laboratory tests in adult patients with hypertrophic cardiomyopathy

**ESC HCM GUIDELINES 2014**

| Serum immunoglobulin free light chain assay, serum and urine immunofixation, and urine electrophoresis | Should be considered if amyloidosis is suspected from history and non-invasive tests. Confirmation of the diagnosis usually requires histological analysis. | AMYLOIDOISIS |
Plasma cell dyscrasia

Biopsies

- **AL amyloid**, is derived from monoclonal immunoglobulin light chains associated with plasma cell dyscrasias

**Biochemical tests**

- to detect the abnormal clonal immunoglobulin production
### Neuromuscular disorders with cardiac involvement

<table>
<thead>
<tr>
<th>Mitochondrial Disorders</th>
<th>Clinical manifestations</th>
<th>Cardiac manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kearns-Sayre</td>
<td>Progressive external ophthalmoplegia, pigmentary degeneration of the retina, short stature, cerebellar ataxia, dementia</td>
<td>AV conduction abnormalities, AV conduction block</td>
</tr>
<tr>
<td>MELAS</td>
<td>Stroke like episodes, lactate acidosis, seizures, dementia</td>
<td>LV hypertrophy, Dilated cardiomyopathy</td>
</tr>
<tr>
<td>MERFF</td>
<td>Ataxic and myoclonic seizures, cerebellar ataxia, progressive muscular weakness</td>
<td>LV hypertrophy, Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Friedreich’s ataxia</td>
<td>Cerebellar ataxia, dysarthria, loss of proprioception, lower extremities muscle weakness, extensor plantar response, areflexia, diabetes mellitus</td>
<td>LV hypertrophy, Atrial fibrillation, Late Q waves on ECG, Sudden cardiac death</td>
</tr>
</tbody>
</table>

- **Electrical**
- **Structural**
Desmin-related cardiomyopathies

- RCM associated with elevated CK levels.

RAPEZZI ET AL
EUR HEART J 2012
What is personalised/stratified medicine?

“Stratified medicine is based on identifying subgroups of patients with distinct mechanisms of disease, or particular responses to treatments. This allows us to identify and develop treatments that are effective for particular groups of patients. Ultimately stratified medicine will ensure that the right patient gets the right treatment at the right time.”

http://www.mrc.ac.uk/research/initiatives/stratified-medicine/
LVH gray zone

• HCM
• HPT
• ATHLETIC HEART

SPECIAL TYPES OF HCM
• SARCOMERIC
• STORAGE - FABRY, POMPE
• INFILTRATION - AMYLOIDOSIS
• INFLAMMATORY – CONNECTIVE TISSUE

• TUMORS
LVH

RED FLAGS

- ATHLETES
- VALVE DISEASE
- HPT
- HCM SUBTYPES

TAKE HOME MESSAGE
LVH GRAY ZONE
SEARCHING BEYOND THE MORPHOLOGY

MORPHOLOGY
imaging technics plus ECG
Are ESSENTIAL

CLINICALLY
ECG
ECHO
HOLTER
c/p EX TEST
MRI – LGE
LAB TESTS

INTERNIST
PEDIATRICIAN
NEUROLOGIST
GENETICIST

EARLY
MULTIDISCIPLINARY
NETWORK