Sudden Cardiac Death in Hypertrophic Cardiomyopathy: Risk Stratification and the Role of Molecular Genetics
OVERVIEW

Background information about HCM

Risk stratification for Sudden Cardiac Death in HCM

- Epidemiology
- Risk factors according to the guidelines
  - Extent of left ventricular hypertrophy
  - Fibrosis in Cardiac Magnetic Resonance Imaging

Molecular Genetics in HCM

- Genetics in HCM in general
- Influence on risk stratification for Sudden Cardiac Death
HYPERTROPHIC CARDIOMYOPATHY: HISTO-PATHOLOGY
HYPERTROPHY, FIBRE DISARRAY, FIBROSIS, SMALL VESSEL DISEASE
# Hypertrophic Cardiomyopathy: Associated Issues

<table>
<thead>
<tr>
<th>Issue</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVOT obstruction</td>
<td>(25%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>(25%)</td>
</tr>
<tr>
<td>Diastolic dysfunction (&gt;50%)</td>
<td></td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>(20%)</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>(1%/year)</td>
</tr>
</tbody>
</table>

**Abnormal ECG**

- ST & T wave abnormality, consider inferolateral ischemia
- Prolonged QT

**ECG Details**

- *7.1.1 12SL 235 CID: 32*

**Demographics**

- Male
- Room: Loc: 378
- 16-SEP-1968 (38 yr)

**Test Information**

- Technician: KRSTYNA ZON
- Test ind: HCM

**References**

Maron et al., JAMA 1999;281(7):650-655
HYPERTROPHIC CARDIOMYOPATHY:
RISK OF SUDDEN CARDIAC DEATH

Although not always the case, massive hypertrophy of the intraventricular septum is common in hypertrophic cardiomyopathy.

Hypertrophic cardiomyopathy is the most common cause of sudden cardiac death in young athletes. Although athletes may have prodromal symptoms of presyncope, an initial presentation of sudden loss of consciousness is common in these individuals.
HYPERTROPHIC CARDIOMYOPATHY: CARDIAC CAUSES OF DEATH IN ATHLETES

- HCM: 36%
- LVH: 8%
- Coronary anomalies: 17%
- Mitral valve prolaps: 4%
- ARVC: 4%
- Myocarditis: 6%
- Coronary anomalies: 17%
- Tunneled LAD: 4%
- Mitral valve prolapse: 4%
- ARVC: 4%
- Myocarditis: 6%
- Coronary anomalies: 17%
- LVH: 8%
- HCM: 36%

Mont et al, Heart 2010, 398-405
Corrado et al, NEJM 1998: 364-369
HYPERTROPHIC CARDIOMYOPATHY: CARDIAC CAUSES OF DEATH IN ATHLETES

- HCM 36%
- Coronary anomalies 17%
- LVH 8%
- Normal heart 3%
- Congenital Other 3%
- DCM 2%
- AS 3%
- CAD 3%
- Tunneled LAD 4%
- Mitral valve prolaps 4%
- ARVC 4%
- Sarcoidosis 1%
- Myocarditis 6%
- Aortic rupture 2%
- Coronary anomalies 17%
- Channelopathies 2%

Mont et al, Heart 2010, 398-405
Corrado et al, NEJM 1998: 364-369
HYPERTROPHIC CARDIOMYOPATHY: SUDDEN CARDIAC DEATH AND EPIDEMIOLOGY

Mode of death
- Sudden
- Heart failure
- Stroke
- All HCM-Related

Annual HCM Mortality

Age at initial Evaluation (years)
- 5-15
- 16-25
- 26-35
- 36-45
- 46-55
- 56-65
- 66-75
- >75

n = 744; mean FU = 8 ± 7 years; annual SCD-rate = 0.7%

Maron BJ et al, Circulation 2000;102:858-864
HYPERTROPHIC CARDIOMYOPATHY:
SUDDEN CARDIAC DEATH AND RISK STRATIFICATION

CARDIAC ARREST
FH FOR SCD
MASSIVE LVH
SYNCOPE

NSVT
ABNORMAL BP RESPONSE

LV APICAL ANEURYSMS
MYOCARDIAL FIBROSIS
MULTIPLE MUTATIONS
END-STAGE

event rate 3%/y

HIGHEST

ICD

Maron BJ et al, J Cardiovasc Electrophsiol 2008;19:1118-1126
HYPERTROPHIC CARDIOMYOPATHY: RISK STRATIFICATION FOR SUDDEN CARDIAC DEATH

Indications For ICD
- Aborted sudden death
- Sustained VT

Major Risk Factors
- LV wall thickness 30mm or greater
- First degree family member SCD
- Recent unexplained syncope

Minor Risk Factors
- Abnormal BP response to exercise
- Non sustained VT on Holter

Modifiers
- CMR: LGE
- LVOT obstruction
- Apical LV aneurysm
- Genetic mutations (double and compound)

AHA/ACC Guidelines, Circulation 2011;124:2761-2791
HYPERTROPHIC CARDIOMYOPATHY: RISK STRATIFICATION FOR SUDDEN CARDIAC DEATH

**Indications For ICD**
- Aborted sudden death
- Sustained VT

**Major Risk Factors**
- LV wall thickness 30mm or greater
- First degree family member SCD
- Recent unexplained syncope

**Minor Risk Factors**
- Abnormal BP response to exercise
- Non sustained VT on Holter

**Modifiers**
- CMR: LGE
- LVOT obstruction
- Apical LV aneurysm
- Genetic mutations (double and compound)

AHA/ACC Guidelines, Circulation 2011;124:2761-2791
HYPERTROPHIC CARDIOMYOPATHY: No RISK FACTORS AND SCD EVENT RATE

- Annual rate of SCD / appropriate ICD shocks
- Number of risk factors
- N = 1606
- 11712 patient years
- Median 6.6 years

O’Mahony, Heart 2013-303271
HYPERTROPHIC CARDIomyopathy: SCD: LEFT-Ventricular hypertrophy

Left-ventricular wall thickness (mm)
- ≤ 15mm
- 16-19
- 20-24
- 25-29
- ≥ 30

Follow-up (years)

Percentage of Patients without sudden death

Spirito et al., NEJM 2000;342:1778-85
HYPERTROPHIC CARDIOMYOPATHY: SUDDEN CARDIAC DEATH AND FIBROSIS
HYPERTROPHIC CARDIOMYOPATHY
GENETICS BASICS

- autosomal dominant
- 1:500 with HCM in general population

1 β-Myosin heavy chain
2 Myosin-binding protein-C
3 Myosin light chain 2 and 3
4 Troponin T
5 Troponin I
6 Tropomyosin
7 Actin

Phenocopies
- Fabry’s disease
- PRKAG2 cardiomyopathy
- Danon’s disease

HYPERTROPHIC CARDIOMYOPATHY
GENETICS BASICS

- No mutation: 50%
- Tropomyosin: 7%
- Troponin T: 7%
- Beta-myosin heavy chain: 15%
- Myosin-binding protein C: 15%
- Others: 6%
- Troponin I
- Troponin C
- Actin
- Myosin light chains

60 – 80%

Maron BJ et al, JACC 2012;60:705-15
Gruner C et al, Circ CV Genetics 2012: epub
HYPERTROPHIC CARDIOMYOPATHY
CURRENT ROLES OF GENETIC TESTING

FAMILY SCREENING
Identification of family members at risk for HCM

Fabry disease
PRKAG2 cardiomyopathy

EXCLUSION OF PHENOCOPIES

AHA/ACC Guidelines, Circulation 2011;124:2761-2791
Sudden Death due to Troponin T Mutations

A new mutation of the cardiac troponin T gene causing familial hypertrophic cardiomyopathy without left ventricular hypertrophy

A Varnava, C Baboonian, F Davison, L de Cruz, P M Elliott, M J Davies, W J McKenna
# HYPERTROPHIC CARDIOMYOPATHY
## GENETICS AND RISK STRATIFICATION FOR SCD

**Long-Term Outcomes in Hypertrophic Cardiomyopathy Caused by Mutations in the Cardiac Troponin T Gene**

<table>
<thead>
<tr>
<th>Adults (n=71)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td>36 (51%)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>37 ± 14</td>
</tr>
<tr>
<td><strong>NYHA I-II</strong></td>
<td>59 (95%)</td>
</tr>
<tr>
<td><strong>Obstruction</strong></td>
<td>6 (9%)</td>
</tr>
<tr>
<td><strong>Maximal wall thickness (mm)</strong></td>
<td>19 ± 5</td>
</tr>
<tr>
<td><strong>SCD in first degree relative</strong></td>
<td>27 (50%)</td>
</tr>
<tr>
<td><strong>Non sustained VTs</strong></td>
<td>13 (24%)</td>
</tr>
<tr>
<td><strong>Maximal wall thickness ≥30mm</strong></td>
<td>3 (5%)</td>
</tr>
<tr>
<td><strong>Syncope</strong></td>
<td>17 (31%)</td>
</tr>
<tr>
<td><strong>Abnormal BP response</strong></td>
<td>26 (48%)</td>
</tr>
</tbody>
</table>

- 552 probands underwent genetic testing
- 20 probands with TNNT2 mutations
- 72 relatives with TNNT2 mutations

Pasquale et al, Circulation CV Gen 2012;5:10-17
HYPERTROPHIC CARDIOMYOPATHY
GENETICS AND RISK STRATIFICATION FOR SCD

Long-Term Outcomes in Hypertrophic Cardiomyopathy Caused by Mutations in the Cardiac Troponin T Gene

Follow up (years)

Cumulative survival

- sudden cardiac death
- CV death

mean FU = 9.9 ± 5.2 years
annual SCD rate = 0.93%

Pasquale et al, Circulation CV Gen 2012;5:10-17
Hypertrophic Cardiomyopathy: Sudden Cardiac Death and Epidemiology

Maron BJ et al, Circulation 2000;102:858-864

Mode of death

- Sudden
- Heart failure
- Stroke

Annual HCM Mortality

n = 744; mean FU = 8 ± 7 years; annual SCD-rate = 0.7%

Annual SCD Rate <1%
HYPERTROPHIC CARDIOMYOPATHY
GENOTYPE - PHENOTYPE
= NO HIGH RISK MUTATIONS
GENOTYPE - PHENOTYPE
= NO CORRELATION
HYPERTROPHIC CARDIOMYOPATHY
GENETICS AND RISK STRATIFICATION FOR SCD: MULTIPLE MUTATIONS

≥ 2 disease causing sarcomere protein gene mutations (double or compound), 5% in genetically tested HCM populations

- Early disease onset
- Marked left ventricular hypertrophy
- Advanced heart failure due to systolic dysfunction
- More frequent SCD events

MULTIPLE MUTATIONS SHOULD BE CONSIDERED AS MODIFYING RISK FACTOR FOR SCD

Maron BJ et al, Heart Rhythm 2012;9:57-63
Girolami et al, JACC 2010;55:1444-53
AHA/ACC Guidelines, Circulation 2011;124:2761-2791
CONCLUSIONS

- Key role of genetics in HCM today: **family screening**, exclusion of **phenocopies**

- **No genotype-phenotype correlation**, essentially, genetics are not part of risk stratification for SCD in HCM, **no high-risk mutations**

- **Multiple mutations** should be considered as modifying risk factor, especially in the absence of conventional risk factors

- **Classic risk factors**: MWTH, unexplained syncope, positive family history for SCD, NSVTs, abnormal BP response

- **Myocardial fibrosis**: modifying risk factor
Thank You

Hypertrophic Cardiomyopathy Clinic
University Hospital Zurich
christiane.gruner@usz.ch