Syncope in Patients with Structural Heart Disease

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Syncope

✓ Common
✓ Frequently benign but ...
✓ ...occasionally due to a potentially life threatening disorder
✓ Diagnosis of the mechanism can be challenging
## Causes of syncope by age

### Younger patient
- ✓ Neurocardiogenic*
- ✓ Psychiatric*
- ✓ LQTS\(^\gamma\)
- ✓ Brugada syndrome\(^\gamma\)
- ✓ WPW syndrome (AF)\(^\gamma\)
- ✓ ARVD\(^\gamma\)
- ✓ HOCM\(^\gamma\)

*usually benign

### Older patient
- ✓ Cardiac \(^\dagger\)
  - ❖ Mechanical
  - ❖ Arrhythmic (tachy or brady)
- ✓ Orthostatic hypotension*
- ✓ Drug related*
- ✓ Multifactorial*

\(^\gamma\) infrequent but not benign
\(^\dagger\) generally not benign
Evaluation of syncope

✔ Establish the cause/mechanism of the syncopal event
✔ Risk stratification of the patient
  ➢ identify those who are at high risk of sudden cardiac death
  ➢ identify those at risk of recurrent syncope and physical injury
High risk of sudden death after syncope

- Severe structural or coronary heart disease
  - Heart failure
  - Low EF
  - Previous myocardial infarction

- Clinical or ECG features suggesting arrhythmic syncope
  - Syncope during exertion or while supine
  - Preceding palpitations
  - Non sustained VT
  - Bifascicular block or IVCD (QRS > 120 ms)
  - Pre-exited QRS complex
  - Prolonged or short QT
  - Brugada pattern
  - Negative T waves in precordial leads, epsilon waves
## Mortality by Cause of Syncope

<table>
<thead>
<tr>
<th>Author (N)</th>
<th>F/U (mos)</th>
<th>Cardiac Cause</th>
<th>Noncardiac Cause</th>
<th>Unknown</th>
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<tbody>
<tr>
<td>Day (198)</td>
<td>12</td>
<td>33</td>
<td></td>
<td></td>
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<tr>
<td>Silverstein (108)</td>
<td>12</td>
<td>19</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Kapoor (204) (1983)</td>
<td>12</td>
<td>30</td>
<td>12</td>
<td>6</td>
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<tr>
<td>Martin (170)</td>
<td>&lt;6</td>
<td>30</td>
<td>1</td>
<td>1.5</td>
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<tr>
<td>Kapoor (433) (1990)</td>
<td>12</td>
<td>26</td>
<td>8</td>
<td>6</td>
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<td></td>
<td>60</td>
<td>50</td>
<td>31</td>
<td>24</td>
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</table>
Structural heart disease that can cause syncope

- Ischemic heart disease
- Non-ischemic dilated cardiomyopathy
- Aortic stenosis
- Hypertrophic cardiomyopathy
- Arrhythmogenic right ventricular dysplasia
- (Primary electrophysiologic disorders – LQTS, Brugada, CPVT)
- Myocarditis
- Pulmonary embolism
- Cardiac tamponade
- Atrial myxoma
- Severe pulmonary hypertension
- Aortic dissection
- Congenital heart disease and certain congenital heart disease repairs
Cardiac syncope

✓ Arrhythmias are the most common cause of cardiac syncope
✓ Tachycardia vs bradycardia (tachy-brady syndrome)
✓ Factors that are contributory to whether a tachyarrhythmia causes syncope or not
  - SVT vs VT
  - Heart rate during arrhythmia
  - Left ventricular function
  - Posture
  - Use of vasoactive drugs
History suggesting cardiac cause of syncope

- Circumstances of the event
  - Exercise
  - Supine
- Prodromal symptoms
  - Chest pain
  - Acute shortness of breath
  - Palpitations
  - Acute onset dizziness

- Presence of definite structural heart disease
- Family history of sudden cardiac death especially at a young age (HOCM, ARVD, primary electrophysiologic disorders)
Physical exam

- Blood pressure (supine and standing) and pulse
- Cardiac exam (displaced PMI, murmur, $S_3$, $S_4$)
- Lung exam – rales
- Respiratory rate and pattern
- Jugular venous distension
- Carotid pulse, CSM
Twelve lead EKG

- Rhythm
- ST elevation
- Q waves
- QT interval
- Brugada pattern
- Delta wave
- LVH pattern
- BBB, AVB, SSS
- T wave inversion in the antero-septal leads, epsilon waves
Strongest predictors of arrhythmic syncope

Predictors of Cardiac Arrhythmias in Patients with Unexplained Syncope

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Abnormal ECG</td>
<td>11.6</td>
<td>4.6–29.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>13.4</td>
<td>3.0–58.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>8.6</td>
<td>3.5–21.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>4.3</td>
<td>1.7–10.9</td>
<td>0.003</td>
</tr>
<tr>
<td>History of cardiac disease (any type)</td>
<td>4.3</td>
<td>1.8–10.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

# Risk Stratification Scores

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk factors</th>
<th>Score</th>
<th>Endpoints</th>
<th>Results (validation cohort)</th>
</tr>
</thead>
</table>
| S. Francisco Syncope Rule\(^{44}\) | - Abnormal ECG  
- Congestive heart failure  
- Shortness of breath  
- Haematocrit < 30%  
- Systolic blood pressure < 90 mmHg | No risk = 0 item  
Risk ≥ 1 item | Serious events at 7 days | 98% sensitive and 56% specific |
| Martin et al \(^{49}\) | - Abnormal ECG  
- History of ventricular arrhythmia  
- History of congestive heart failure  
- Age > 45 years | 0 to 4 (1 point each item) | 1-year severe arrhythmias or arrhythmic death | 5% score 1  
16% score 2  
27% score 3 or 4 |
| OESIL score\(^{41}\) | - Abnormal ECG  
- History of cardiovascular disease  
- Lack of prodrome  
- Age > 65 years | 0 to 4 (1 point each item) | 1-year total mortality | 0% score 0  
0.6% score 1  
14% score 2  
29% score 3  
53% score 4 |
| EG SYS score\(^{42}\) | - Palpitations before syncope (+4)  
- Abnormal ECG and/or heart disease (+3)  
- Syncope during effort (+3)  
- Syncope while supine (+2)  
- Autonomic prodrome\(^{3}\) (-1)  
- Predisposing and/or precipitating factors\(^{9}\) (-1) | Sum of + and − points | 2-year total mortality | Cardiac syncope probability  
2% score < 3  
13% score 3  
33% score 4  
77% score > 4 |
Blood tests are generally not helpful for diagnosis of a cardiac cause of syncope, but should include evaluation for anemia, electrolyte disturbances and in selected cases cardiac biomarkers.
Echocardiogram

- Clinical suspicion of structural heart disease or syncope secondary to cardiovascular cause
- Previous or known heart disease
- Plays an important role in risk stratification based on EF
Syncope in patients with ischemic heart disease

- Myocardial ischemia
- Ventricular tachyarrhythmias (scar related – monomorphomic- or due to acute ischemia - polymorphic)
- Bradyarrhythmias (ischemia/drugs)
- Orthostatic hypotension
Syncope and coronary artery disease

✓ The work up of patients with syncope and who are at risk of coronary artery disease should include evaluation for myocardial ischemia

✓ In elderly patients, syncope can be the only presenting symptom of myocardial infarction
Syncope and coronary artery disease

- In patients with syncope, coronary artery disease and a severely depressed EF an ICD is indicated according to the ESC guidelines, regardless of the perceived etiology of the event.
- In this cohort, an electrophysiology study is no longer indicated for risk stratification.
Electrophysiology study
Electrophysiologic testing in patients with syncope and coronary artery disease

✓ If there is a history of prior myocardial infarction and preserved EF, cardiac electrophysiology study may be indicated for further risk stratification

✓ Inducibility is associated with high mortality and non-inducibility predicts low risk of SCD
Syncope and non ischemic dilated cardiomyopathy (DCM)

✓ Potential causes include arrhythmias and orthostatic hypotension
✓ 45% of patients with DCM, class III and IV, who presented with syncope died suddenly within one year vs 12% of those who did not have syncope*
✓ 70% of patients with DCM who presented with VT or SCD had a prior syncopal spell*
✓ Inducibility of VT/VF during EP study not predictive of future risk

ICDs in high risk syncope patients

- ICD treated patients remain at risk for syncope because only the sudden cardiac death risk is being addressed.
- This implies the need for identification of the precise mechanism of syncope in these patients and specific treatment as far as is possible.
Hypertrophic cardiomyopathy (HCM)

- Syncope increases the risk of SCD by fivefold in HCM
- Syncope in HCM can be caused by a variety of disorders, including VT, SVT/AF, hypotension associated with exercise and severe outflow tract obstruction
- Other risk factors for SCD may help in risk stratification
  - Family history of SCD
  - Non sustained VT
  - Marked (> 30 mm) LV hypertrophy
  - ↓ BP with exercise
  - Late enhancement on MRI?
- EP study has minimal role in risk stratification
Arrhytmogenic right ventricular dysplasia

- Fibrous and fatty replacement of the myocardium
- Younger individuals – family clustering
- Involves the right ventricle with occasional left ventricular extension
- Inverted T waves in V1-V3, epsilon waves
- Late potentials on SAECG
- RV dilatation and localized RV aneurysm formation on echo/MRI
EKG in RV dysplasia – epsilon waves
RV dysplasia with LV involvement
Could genetic information be useful in the evaluation of patients with unexplained syncope?
A rare variant in *MYH6* is associated with high risk of sick sinus syndrome


Through complementary application of SNP genotyping, whole-genome sequencing and imputation in 38,384 Icelanders, we have discovered a previously unidentified sick sinus syndrome susceptibility gene, *MYH6*, encoding the alpha heavy chain subunit of cardiac myosin. A missense variant in this gene, c.2161C>T, results in the conceptual amino acid substitution p.Arg721Trp, has an allelic frequency of 0.38% in Icelanders and associates with sick sinus syndrome with an odds ratio = 12.53 and *P* = 1.5 x 10^-29. We show that the lifetime risk of being diagnosed with sick sinus syndrome is around 6% for non-carriers of c.2161C>T but is approximately 50% for carriers of the c.2161C>T variant.
Cardiac muscle myosin, along with actin, is one of the major components of the sarcomere, the building block of the contractile system of cardiac muscle.

*MYH6* encodes the alpha-cardiac myosin heavy chain (α-MyHC), one of two sarcomeric MyHC isoforms that are expressed in the mammalian myocardium, and is primarily expressed in the atria.
Penetrance of the SSS mutation

Figure 3  Penetrance of sick sinus syndrome among carriers and non-carriers of c.2161C>T. The red crosses represent observed penetrance of sick sinus syndrome for 10-year birth cohorts among heterozygous carriers of c.2161C>T. The red line represents the fit of the logistic model to the c.2161C>T carrier data. The blue line and crosses represent the same information for non-carriers of c.2161C>T. SSS, sick sinus syndrome.
Syncope

Carriers  Non-carriers

50% diagnosed with SSS  19% diagnosed with SSS

$P = 0.0050$
GWAS of ECG parameters

Several common variants modulate heart rate, PR interval and QRS duration


Electrocardiographic measures are indicative of the function of the cardiac conduction system. To search for sequence variants that modulate heart rate, PR interval and QRS duration in individuals of European descent, we performed a genome-wide association study in ~10,000 individuals and followed up the top signals in an additional ~10,000 individuals. We identified several genome-wide significant associations (with $P < 1.6 \times 10^{-7}$). We identified one locus for heart rate ($MYH6$), four for PR interval ($TBX5$, $SCN10A$, $CAV1$ and $ARHGAP24$) and four for QRS duration ($TBX5$, $SCN10A$, $6p21$ and $10q21$). We tested for association between these loci and subjects with selected arrhythmias in Icelandic and Norwegian case-control sample sets. We observed correlations between $TBX5$ and $CAV1$ and atrial fibrillation ($P = 4.0 \times 10^{-13}$ and $P = 0.00032$, respectively), between $TBX5$ and advanced atrioventricular block ($P = 0.0067$), and between $SCN10A$ and pacemaker implantation ($P = 0.0029$). We also replicated previously described associations with the QT interval.

<table>
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<tr>
<th>Locus</th>
<th>Gene</th>
<th>SNP</th>
<th>HR</th>
<th>PR</th>
<th>PR</th>
<th>QRS</th>
<th>AF</th>
<th>PM</th>
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</table>
Holter monitor data for genetic studies of electrophysiologic variables

- Atrial extrasystoles
- Ventricular extrasystoles
- Supraventricular tachycardias
- Sinus pauses / sinus arrest
- Atrioventricular block
- Ventricular tachycardia
- Heart rate
- Heart rate variability
- Supraventricular tachycardias
Syncope

History, physical examination, electrocardiogram

Diagnostic

Unexplained syncope

Echocardiogram, exercise test, Holter monitoring

Diagnostic

Non diagnostic

No further work-up unless additional episodes

Event monitor or implantable loop recorder

Genetic Testing?
Summary

✓ In patients with syncope the presence of structural heart disease should be considered and further evaluation performed as indicated

✓ The presence of structural heart disease in syncope is associated with a worse prognosis and may be a predictor of sudden cardiac death

✓ It is always useful to inquire about family history of sudden death in the evaluation of patients with syncope