Investigation of Sudden Cardiac Death in New Zealand

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How common is Sudden Cardiac Death?

• Estimated to be between 1 to 7 per 100,000 people (Aged 1-35y)

• 150 deaths of young people per year in NZ (non-SIDS)

• 20-50% of deaths are due to inherited cardiomyopathies or channelopathies

• Many of these deaths may be preventable
  – Trigger avoidance, beta-blockers, sympathectomy, ICD, etc.

Earle NZ Med J 2016;129:7066
Sudden Cardiac Death

- **Aborted SCD**
  - Proband is alive
  - Able to have their physiology investigated
    - ECG, ETT, Echo, MRI, drug challenge
  - Able to have their anatomy investigated
    - Angio, Echo, MRI
  - Genetic investigation of proband

- **Sudden death**
  - Proband
  - Not able to have physiology investigate
  - Thorough anatomical investigation at autopsy
  - Negative autopsy means family is critical to investigation
    - Anatomy
    - Physiology
  - Genetic investigation of family
    - Parents are important

Cardiac Inherited Conditions

**Channelopathies**
- Long QT Syndrome
- Catecholaminergic polymorphic ventricular tachycardia (CPVT)
- Brugada Syndrome
- Short QT Syndrome
- Progressive cardiac conduction disease

**Cardiomyopathies**
- Hypertrophic cardiomyopathy
- Familial dilated cardiomyopathy
- Arrhythmogenic right ventricular cardiomyopathy (ARVC)
- Left Ventricular Non-Compaction cardiomyopathy
Causes of Sudden Cardiac Death in the Young (1-40y)

Sudden Cardiac Death (0-40 years)

- Cause identified (~70%)
  - Coronary Artery Disease (25%)
    - HCM (15-10%)
  - Myocarditis (5-10%)
  - Structural Heart Disease
    - Others
- No cause identified (i.e., SADS (~30%))
  - Arrhythmogenic Disease
    - LQTS (15-20%)
    - CPVT (15-20%)
  - Others

Figure 1: Causes of sudden cardiac death in the young (0-40 years). Based on postmortem findings, SADS, sudden arrhythmic death syndrome; LQTS, long-QT syndrome; CPVT1, catecholaminergic polymorphic ventricular tachycardia type 1; HCM, hypertrophic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy. Others includes SIDS cases. Approximate proportion of cases shown as (%) within each category.

Semsarian EHJ 2015; 36:1290

Causes of Sudden Cardiac Death in Young (AUS)

- Other (11%)
- Congenital heart disease (7%)
- Myocarditis (12%)
- HCM / Unexplained LVH (15%)
- Coronary artery disease (24%)
- SUD (probable primary arrhythmogenic) (31%)

Semsarian Heart Rhythm 2012;9:145
How common is Sudden Unexplained Death?

Criteria for ‘negative autopsy’

- Structurally normal heart
- No abnormal histopathological findings
- No other cause of death identified at post-mortem
  - e.g. pulmonary embolus
- Normal toxicology screen
- No pre-death clinical features to suggest other cause of sudden death
  - e.g. epilepsy
Multi-disciplinary approach

Figure 4 Specialized multidisciplinary approach to care of families with sudden cardiac death in the young, PCP, primary care physician. Adapted from Ingles et al.14

Suggested Algorithm for Investigating Families

Figure 3 Clinical investigation pathway of surviving family members where no cause of death is identified. CMR, cardiac magnetic resonance; ECG, electrocardiogram; SAECG, signal-averaged ECG. Pharmacological challenge includes sodium channel blocker and epinephrine testing. If symptoms develop in relative or new information becomes available in the family, then further review indicated. Adults are generally followed up to age 40 years when most primary genetic heart diseases are phenotypically expressed. Modified from Priori et al.15
Ajmaline Challenge

Adenosine Challenge

Adrenaline testing – LQTS and CPVT

Figure 2. Cases where diagnosis was made through pharmacologic tests. (A) Epinephrine test results positive for LQTS in the proband with a mutation in KCNH2 (Pro347Ser). Note the slight elongation of the absolute QT interval with a notch in the ascending limb of the T wave. (B) Epinephrine test results positive for CPVT in a 15-year-old boy with exercise-induced VF, with de novo mutation in RyR2 (Leu915Trp).
Adrenaline testing for LQTS

Figure 3. A, Change in heart rate-corrected QT interval (QTc) with epinephrine at a dose of ≤0.1 μg · kg⁻¹ · min⁻¹.

Vyas et al. Circulation. 2006;113:1385-1392

Molecular Autopsy

Semsarian EHJ 2015; 36:1290
Phenotype is Critical

- CASPER registry
  - 375 cardiac arrest survivors from 2006 to 2015
  - 174 underwent genetic testing
- Phenotype-negative patients have a lower yield from genetic testing
  - 13%
- Phenotype-positive patients have a greater yield
  - 25-60%

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>n</th>
<th>Pathogenic Variant, %</th>
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<tbody>
<tr>
<td>LQTS</td>
<td>25</td>
<td>5 (20)</td>
</tr>
<tr>
<td>BrS</td>
<td>7</td>
<td>2 (29)</td>
</tr>
<tr>
<td>CPVT</td>
<td>8</td>
<td>2 (25)</td>
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<tr>
<td>ARVC</td>
<td>10</td>
<td>6 (60)</td>
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<tr>
<td>Phenotype negative</td>
<td>102</td>
<td>13 (13)</td>
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</table>

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; and LQTS, Long QT syndrome.

Reclassification of Genetic Results

Variant of Uncertain Significance (VUS) = Genetic Purgatory
236 patients received an ICD at Waikato Hospital in 2014 and 2015
66 were for secondary prevention (post arrest)
48 had cardiac disease which explained event (e.g. ischaemia, cardiomyopathy) and were excluded.
Leaving 18 with no known cause

Aged 20-75, mean = 45 +/- 14y
We looked at investigations after their arrest
Final Diagnoses at 6 month follow up

- 1 x Sarcoidosis
  - Diagnosed with CMR
- 2 x Brugada
  - Diagnosed with Ajmaline
- 2 x Dilated Cardiomyopathy
  - Diagnosed with repeat echo
- 1 x J Wave Syndrome
  - Diagnosed with Ajmaline, ECG & clinical history

Leaving 12 with no known cause.

Investigations of the 12 Undiagnosed Patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Count</th>
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<tbody>
<tr>
<td>Echo</td>
<td>12</td>
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<tr>
<td>Angio/CTCA</td>
<td>11</td>
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<tr>
<td>ETT</td>
<td>8</td>
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<tr>
<td>MRI</td>
<td>9</td>
</tr>
<tr>
<td>Ajmaline</td>
<td>5</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>1</td>
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<tr>
<td>SAECG</td>
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</tbody>
</table>

6 of 12 Registered with CIDG
Investigation of Resuscitated Sudden Cardiac Arrest

- Diagnostic “gap” in investigations
  - Missed opportunity to help the patient
  - Missed opportunity to help their family

  How would your DHB compare with thoroughness of investigations?

Figure 2: New Zealand Cardiac Inherited Disease Registry registrants per 100,000 residents by district health board area.

Figure 3: Clinically diagnosed long QT syndrome registrants per 100,000 residents by district health board area.

CIDG registrants by DHB  LQTS diagnoses by DHB

Earle NZ Med J 2016;129:7066
Refer to CIDG!

- Draw up a family tree
- Disease counselling / education
- Collate cardiology evidence
- Check the proband is not related to another known case in the country
- Arrange family screening for at-risk relatives
  - Needs engagement; family to contact co-ordinator
- Advice regarding genetic testing or not
  - Sort out the wheat (mutations) from the chaff (VUS)
- Pursue gene negative cases clinically
- Cascade test gene positive cases
- You and your patient will be advised of important new developments
- Your case will contribute to understanding the disease and contributes to research

Investigation of Resuscitated Sudden Cardiac Death
After exclusion of Acute Coronary Syndrome and Myocarditis

History
Precise details of event, previous syncope / symptoms

Family History
3-generation family tree, FHx of CID / SCD / Syncope / Epilepsy / Drowning

Initial basic cardiac tests
Daily ECGs
Echo

Blood Tests
Toxicology, metabolic, DNA storage

Diagnosis of a non-hereditary condition

No diagnosis yet
Exclude all possible causes. Involve EP / CIDG

Further cardiac tests
CMR pre ICD
ETT LQT/Sprint Protocol (off beta blockers, if exercise related RSCD)

Pharmacological challenges
Ajmaline
Adrenaline
+- Adenosine

Diagnosis of Inherited Heart Disease

No diagnosis yet
Family investigations (minimum ECG)
Under the age of 40 years, refer CIDG

Refer to CIDG
If patient dies, request autopsy
Investigation of Sudden Cardiac Death in New Zealand

- Common (150/year in NZ) – large impact on families and communities
- Two groups: Aborted SCD and Families of SCD
- Cardiomyopathies and Channelopathies
- Multidisciplinary approach
- Clinical phenotype is very important
  - We can do better at this; more screening tests and referrals
- Genetic tests complement this
  - Make your job easier or make your job harder; to the benefit of patients & their families