Aberrant sodium influx causes cardiomyopathy and atrial fibrillation in mice

Atrial Fibrillation (AF)

Background

CLINICAL CHARACTERISTICS

Prevalence
- 6% of all Americans >65 years
- 15-20% of all strokes

Clinical Presentation
- Many are asymptomatic
- Palpitations, shortness of breath
- Chest pain, fatigue
- Stroke, HF

Clinical Diagnosis - ECG
- Fast and Irregular heart beat

Management of AF
- Pharmacotherapy
- Ablative therapy
- Bioelectric therapy

1. Lone AF
   - < 60 years old
   - No clinical evidence of cardiopulmonary disease

2. Paroxysmal AF
   - 24 hours to a week

3. Persistent AF
   - Lasting more than a week

4. Permanent AF
   - Chronic
1. Shortening of Atrial Effective Refractory Period (ERP)
   - Enables Reentry wavelets

2. Action Potential Duration (APD) prolongation
   - Early after depolarizations (EADs)
   - Delayed after depolarizations (DADs)
   - Premature beats
Research Objectives

1. Role of persistent Na current
   - Atrial enlargement
   - Dilated Cardiomyopathy
   - Spontaneous AF

2. Mouse model of AF
   - Spontaneous and prolonged AF
1. **Mouse Model**
   - F1759A line engineered with lidocaine resistant SCN5A

2. **Telemetry and ECG**
   - Absence of P waves and irregular RR intervals

3. **Quantitative PCR**
   - Combined expression of mouse and human Scn5A

4. **Immunoblots and Immunofluorescence**
   - Anti-FLAG, anti-Nav1.5, anti-tubulin antibodies

5. **Cellular Electrophysiology**
   - Cells isolated from 2 month mice with AF
   - TTX sensitive persistent Na current

6. **Ca transients**
   - Cells loaded with Fura-2/AM

7. **Echocardiography**
   - Left atrial diameter, LVEDD, LVEF measured

8. **Histology**
   - 10 micron slices examined

9. **Transmission Electron Microscopy**
   - 60 nm slices examined

10. **Epicardial Optical Mapping**
    - 4- to 12 month old F1759A-dTG
    - DF, RI

11. **Statistics**
    - Unpaired 2-tailed t-test
Cardiac specific, FLAG-tagged F1759A-Na$_v$1.5 expressing TG mice

**Results**

![Diagram showing the expression of F1759A-Na$_v$1.5 in cardiac tissue.](image)

**B**

<table>
<thead>
<tr>
<th>mRNA EXPRESSION (Normalized NTG)</th>
<th>Ventricle</th>
<th>Atrium</th>
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<tbody>
<tr>
<td>Mouse Scn5a</td>
<td>1.5</td>
<td>2.0</td>
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<tr>
<td>Mouse Scn5a + human SCN5A</td>
<td>2.5</td>
<td>3.0</td>
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**C**

- **Anti-FLAG Ab:**
  - Positive staining
  - Negative staining

- **No anti-FLAG Ab:**
  - Positive staining

**D**

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<th>F1759A rtTA</th>
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**Western Blots**

- **FLAG:**
  - Ventricular smear
  - Atrial smear
- **Nav:**
  - Ventricular smear
  - Atrial smear
- **Tubulin:**
  - Ventricular smear
  - Atrial smear
F1759A-Nav1.5 increases persistent Na current in atria and ventricles
Increased Na influx sufficient to cause atrial and ventricular cardiomyopathy

Results
Prolonged QT interval and spontaneous AF in F1759A-dTG mice
Results

Surface optical voltage mapping of AF
Inhibition of NCX attenuates atrial and ventricular arrhythmogenesis in F1759A-dTG mice

Results

[Graphs and diagrams illustrating the effects of inhibition of NCX on atrial and ventricular arrhythmogenesis in F1759A-dTG mice.]
1. **F1759A-dTG mice can produce spontaneous and prolonged episodes of AF (rotors, and waves)**
   - Atrial arrhythmias (short episodes) could only be elicited by aggressive burst pacing in other mouse models
   - KPQ mice, and TG mice lines unable to produce spontaneous or sustained AF episodes

2. **F1759A-dTG mice mimics the structural and functional abnormalities due to persistent Na current**
   - Prolongation and dispersion of APD
   - Increased intracellular Ca, via reverse mode NCX
   - Chamber enlargement, fibrosis, and mitochondrial injury

3. **Inhibiting NCX in reverse mode reduced spontaneous atrial and ventricular arrhythmias**
   - Targets downstream effects of enhanced Na entry
1. **Mouse vs Human model**
   - Mouse has different cardiac ion channel profile compared to humans
   - Higher basal heart rate
**What did they do?**

Investigate the role of persistent Na current on structural and EP perturbations leading to AF in mice.

**What did they find?**

Incomplete Na channel inactivation results in:
- Atrial and ventricular enlargement
- Myofibril disarray
- Fibrosis and mitochondrial injury
- EP dysfunction
- Spontaneous and prolonged AF

**What’s next?**

- F1759A-dTG mice model for studying arrhythmia mechanisms

**What does it mean?**

- **Persistent Na current** can explain AF mechanisms (rotors, wavelets)
- **Inhibition of NCX** could be a target for AF therapy