Functional Role of the His-Purkinje System in Arrhythmogenesis

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<table>
<thead>
<tr>
<th>Condition</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bundle branch reentry</td>
<td>Haissaguerre et al, <em>Lancet</em> 2002</td>
</tr>
<tr>
<td>Multifocal PVCs</td>
<td>Laurent et al, <em>JACC</em>, 2012</td>
</tr>
</tbody>
</table>
The Purkinje Network

Johannes Purkinje (1787-1869)  Sunao Tawara (1873-1952)

Human Purkinje fiber network as drawn by Tawara (1906)

Murine Purkinje network as visualized by the Cntn2-eGFP reporter (2014)

Maass et al, Stem Cells. 2014
What’s Unique about Purkinje Cells?

- The absence of T-tubules
- Distinctive mitochondria
- Large glycogen density
- Faster conduction velocity (x3)
- Large conductance Cx43 and Cx40
- Faster upstroke velocity ($dV/dt_{\text{max}}$) of action potential
- Pronounced early repolarization (Phase 1) more negative plateau potential
- Larger action potential amplitude
- Longer action potential duration and refractoriness
- 3 kinds of Ca2+ release channels in the membrane of the ER
  - IP3R, RyR2 and RyR3

Michel Haissaguerre, Nature review 2016
Purkinje cell

cardiac muscle

Purkinje fibers
Functional diversity in the heart

- **Pacemaker cells (impulse formation)**
  - Channels: HCN4 ++, Cx45 +, Cx30.2 ++

- **Atrial myocytes (rapid activation and contraction)**
  - Channels: Nav1.5 +++, Cx40 ++++

- **Purkinje cells (extremely rapid conduction & pacemaker activity)**
  - Channels: Nav1.5 ++++, Cx40 ++++

- **Ventricular myocytes (synchronized contraction)**
  - Channels: HCN2/4 ++, Cav3.x (T-type) ++, Nav1.5 ++, Cx43 +++

**Diagram elements:**
- Right atrium
- Left atrium
- Right ventricle
- Left ventricle
- Fibroblasts
- Endocardial layer

**Diagram labels:**
- AV node
- SA node
- Purkinje fibers
• The inositol trisphosphate receptor (IP3R1) antibody (green)
• The RyR2-specific antibody (red)
• There is a gap in IP3R1 and RyR2 staining (arrow)
• This gap was filled by the RyR3 antibody.

*Circ. Res. 97, 35–43 (2005)*
Automaticity and Triggered activity

• Automaticity, pacemaker activity
  – slow diastolic depolarization during phase 4 (I_f current)
  – Na^+-Ca^{2+} exchange and Ca^{2+} mediated Cl^- channel
  – Not single Purkinje cells
  – Ex. Myocardial infarction
Ca$^{2+}$ transients in Purkinje cells

A. AP evoked Ca$^{2+}$ transients
B. Spontaneous cell-wide Ca$^{2+}$ wave

Cardiovasc Res. 2003; 57:681-93
Purkinje-muscle junctions

Transitional cells

- Delay in the anterograde conduction (3-12ms)
- Short conduction delay of the retrograde conduction (1ms)
- Preferential anterograde block

Circulation Research 1991;69:429-437
Purkinje-muscle junctions

- Overcome the large electrical source-load mismatch
- APD
  - Gradually longer in peripheral sites (Max APD at 2-3mm to terminal)
  - Prevent retrograde conduction
- Unidirectional block, re-entry formation in pathologic status

Circ Res.1998;82:1063-1077.)
Complex Structure and Function of Purkinje cells

- Complex arborization of Purkinje network
- Longer APD
- Complex junctions between Purkinje fibers and ventricular muscle
- Longest APD at junction
- Specific cellular architecture of Purkinje fibers
- Spontaneous Ca2 waves can occur spontaneously

Tawara, Desmoulins, Tranum-Jensen, Myerburg, Boyden, Stuyvers
PURKINJE RELATED ARRHYTHMIA
a Myocardial infarction (74/M)

b HCMP (23/F)

c ECG monitoring (equivalent to ECG lead I) DCMP with LBBB (42/F)

### Spectrum of Purkinje-related arrhythmias

<table>
<thead>
<tr>
<th>Type of arrhythmia</th>
<th>Pathological causes</th>
<th>Prevalence</th>
<th>Ablation target</th>
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<tbody>
<tr>
<td><strong>Monomorphic</strong></td>
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<tr>
<td>Bundle branch re-entry</td>
<td>Nearly constant structural heart disease and pre-existing conduction disorder (prolonged HV interval or bundle branch block)</td>
<td>7% of inducible VT and up to 41% in cardiomyopathies</td>
<td>Right bundle branch</td>
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<td>Other myocardial VTs often present</td>
</tr>
</tbody>
</table>
| Fascicular re-entry         | 90% left posterior fascicle
10% left anterior or septal fascicle
Verapamil-sensitive slow conducting component                                                                                                           | Idiopathic: 10% of idiopathic re-entrant VT                                                                          | Idiopathic: Distal fascicle or slow component
Success rate up to 92% at 9 years                                                                                                                       |                                                                                                                      |
|                             | Associated with scar: 11% of post-MI VT                                                                                                                                                                              | Associated with scar: Fascicular potentials
Within or at the border of scar                                                                                                                          |                                                                                                                      |
| Focal Purkinje VT           | Usually associated with structural heart disease                                                                                                                                                                     | <1% of focal VT                                                                                                     | Earliest focal activity                                                                                 |
| **Polymorphic**             |                                                                                                                                                                                                                      |                                                                                                                      |                                                                                                          |
| Trigger for polymorphic VT/VF | Ischaemic VF, idiopathic VF, and a variety of VF associated with cardiomyopathies and channelopathies (except Brugada syndrome)                                                                           | 50–85% of VF initiations                                                                                             | Distal fascicle / Purkinje–muscle junction
Success rate up to 82% at 5 years                                                                                                                         |
PM reentry initiation

Role of the Purkinje system in triggering VF

- Automatic diastolic depolarization and triggered activity with abnormal Ca$^{2+}$ spark linked to K$^+$ and Ca$^{2+}$

- Triggered activity (EADs or DADs)
  - EADs
    - Phase 2 and 3
    - Reactivation of inward current (L type Ca$^{2+}$ and/or late Na$^+$)
  - DADs
    - Phase 3 and 4
    - Driven by intracellular Ca$^{2+}$ load
    - Large Ca$^{2+}$ waves originating from the ER in direct relation with the Ca$^{2+}$ load
Spontaneous Ca$^{2+}$ activity in Purkinje cells after myocardial infarction.
Role of the Purkinje system in triggering VF

High density mapping (504-electrode array) of VF during first 10 min in canine hearts

Circulation 2007;116:1113-1119
Role of the Purkinje system in triggering VF

Circulation. 2002;106:962-967
<table>
<thead>
<tr>
<th>Type of heart disease</th>
<th>Site of origin of VF in published studies</th>
<th>Site of origin of VF in our experience</th>
<th>Cumulative Purkinje prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structural heart disease</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ischaemic heart disease</td>
<td>60 patients:</td>
<td>25 patients:</td>
<td>77/85 90%</td>
</tr>
<tr>
<td></td>
<td>• 53 from LV Purkinje (84%)</td>
<td>• 22 from LV Purkinje</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Scar-related trigger in six studies23-73,76,82,108,119</td>
<td>• One from myocardium</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Two from myocardium and Purkinje</td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>12 patients60-82;</td>
<td>Three patients:</td>
<td>8/15 53%</td>
</tr>
<tr>
<td></td>
<td>• Six from LV Purkinje (50%), all six scar-related</td>
<td>• Two from LV Purkinje</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• All four catecholamine-induced VF were triggered from Purkinje</td>
<td>• One from myocardium</td>
<td></td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>One patient with two VF triggers from anterior and posterior fascicles, not scar-related120</td>
<td>Four patients:</td>
<td>5/5 100%</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>Three patients with aortic valve disease79,84;</td>
<td>One patient with aortic valve disease, trigger from LV Purkinje</td>
<td>4/4 100%</td>
</tr>
<tr>
<td></td>
<td>• All three from LV Purkinje</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Two patients:</td>
<td>NAD</td>
<td>2/2</td>
</tr>
<tr>
<td></td>
<td>• Both with Purkinje triggers75, no mention of scar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Two patients:</td>
<td>NAD</td>
<td>2/2</td>
</tr>
<tr>
<td></td>
<td>• Both with Purkinje triggers, not scar-related85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac lymphoma</td>
<td>One patient with Purkinje trigger86</td>
<td>NAD</td>
<td>1/1</td>
</tr>
<tr>
<td>LV noncompaction</td>
<td>One patient with Purkinje trigger86</td>
<td>NAD</td>
<td>1/1</td>
</tr>
<tr>
<td><strong>Channelopathies (and described mutations)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPVT (mutations of ryanodine receptor or calsequestrin proteins63)</td>
<td>Three patients89 (A. Nogami, personal communication):</td>
<td>Two patients:</td>
<td>1/5 20%</td>
</tr>
<tr>
<td></td>
<td>• One with Purkinje trigger</td>
<td>• Both multifocal from Purkinje and myocardium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Two with multifocal Purkinje and myocardium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long QT syndrome (&gt;13 ion-channel gene mutations)</td>
<td>Seven patients:</td>
<td>Seven patients:</td>
<td>7/14 50%</td>
</tr>
<tr>
<td></td>
<td>• Two RVOT72,94, one LVOT93, one RV Purkinje, three LV Purkinje (two multifocal)70</td>
<td>• Five from Purkinje (multifocal)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Two from myocardium</td>
<td></td>
</tr>
<tr>
<td>Short QT syndrome (K+-channel gene mutations)</td>
<td>NAD</td>
<td>One patient from LV Purkinje</td>
<td>NAD</td>
</tr>
<tr>
<td>Early repolarization syndrome (rare K+-channel or Ca2+-channel gene mutations)</td>
<td>Seven patients (A. Nogami, personal communication):</td>
<td>22 patients:</td>
<td>24/29 83%</td>
</tr>
<tr>
<td></td>
<td>• Five from RV/LV Purkinje</td>
<td>• 19 from RV/LV Purkinje</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Two from myocardium</td>
<td>• Three from myocardium</td>
<td></td>
</tr>
</tbody>
</table>
Summaries

- Purkinje cell have unique characteristics
  - Long APD
  - Faster Conduction velocity
  - Automaticity, Triggered activity
  - Spontaneous Ca wave
- Purkinje network
  - Sink-load (source) mismatch
  - Transient cell, PM junction
  - Conduction delay
- VF / VT is associated with unique / reentry and non-reentrant mechanism of Purkinje network (cell)
- Purkinje potential (network) may important target of idiopathic VF
EWHA WOMANS UNIVERSITY MEDICAL CENTER