Cardiac Conduction System

Il-Young Oh, MD
• History of cardiac conduction system
  – Purkinje (1839)
  – His (1893)
  – AV node (1906)
  – SA node (1907)
• Myocytes aggregated together, and purported to be responsible specifically for conduction, should be:
  – histologically discrete from adjacent working myocardium,
  – serially traceable from section to section,
  – insulated from the adjacent working myocardium by a sheath of fibrous tissue.
Netter FH. Heart (CIBA Collection of Medical Illustrations, Volume 5): CIBA; 1978.
Anatomy of the tricuspid valve (surgical view through a right atriotomy)
The fibrous skeleton is concentrated at the base of the ventricular mass. It provides electrical insulation at the atrioventricular level and fibrous continuity for the leaflets of the mitral, aortic, and tricuspid valves. Its components include the fibrous trigones, the fibrous area of aortic-mitral continuity, the subvalvar collar of the mitral valve, the membranous septum, the interleaflet triangles, the tendon of Todaro, and likely the conus ligament.
AVN and His bundle

- histologically discrete
- traceable from section to section in serially prepared material
- if to be considered as tracts, should be insulated by fibrous tissue from the adjacent myocytes.

In Masson's trichrome–stained section, the myocytes are stained purple, and connective tissue is stained blue.
Histology of myocytes of ventricular myocardium (B, 1 in A), compact zone (C, 2 in A), transitional zone (D, 3 in A) of AV node, and atrial muscle (E, 4 in A), respectively (bars of B–E=100 μm).
Comparison of AV conduction axis between human and rabbit heart


The distal part of the axis became anatomically discrete as it entered the insulating tissues of the central fibrous body.

Part of the axis was in contact with atrial myocytes.
Regional heterogeneity of the electrical properties of the heart

Atrium vs. Ventricle
- Cav1.3, Cav3.1, Cavα2δ2, Cx40, Navβ1, Kv1.3, Kv1.5, Kv1.6, Kv4.2, Kv4.3, SUR1, KCNE2, KCNE4, KCNE5, SK2, Kir3.1, Kir3.4, TWIK1, TASK1, HCN1, HCN4

V vs. A
- Kv1.4, Kir2.1, PLB, RYR2

Purkinje fibers vs. Ventricle
- Cav1.3, Cav3.1, Cavα2δ2, Cx40, Nav1.7, Kv1.3, Kv1.6, Kv4.3, Kvβ3, KCNE2, KChAP, Kir3.1, TWIK1, TASK1, TASK2, HCN1, HCN3, HCN4, CIC2, CIC6, CALM1, InsP3R1, InsP3R3

V vs. PF
- Cav1.2, Cx43, KCNE5, KChIP2, Kir2.1, Kir2.3, Kir6.1, Kir6.2, NKAα3, NCX1, SERCA2, CASQ2, RYR2

Endocardium vs. Epicardium
- Nav1.5, Navβ1, Kv1.4, Kir3.1

V vs. PF
- Cav1.2, Kv1.2, Kv1.3, KChIP2, SERCA2, CALM3, Calcineurin-α
Currents and channels involved generating resting membrane and action potentials

### Atrial & Ventricular Cells

- $I_{\text{Na}}$
- $I_{\text{Ca-L}}$
- $I_{\text{Ca-T}}$
- $I_{\text{NS}}$
- $I_{\text{Na/Ca}}$

### Sinoatrial Node Cells

- 0 or small
- $I_{\text{Ca-L}}$
- $I_{\text{Ca-T}}$
- $I_{\text{Na/Ca}}$

- $I_f$
- $I_{\text{Na-B}}$
- $I_K$
- $I_{K\cdot G}$
- $I_{\text{pump}}$
- $I_{K\cdot ATP}$

Electric activity of rabbit sinus node.
Properties of Transmembrane Potentials in Heart Cells

<table>
<thead>
<tr>
<th>Property</th>
<th>SA Nodal cell</th>
<th>Atrial myocyte</th>
<th>AV Nodal cell</th>
<th>His Purkinje cell</th>
<th>Ventricular myocyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting potential (mV)</td>
<td>−50 to −60</td>
<td>−80 to −90</td>
<td>−60 to −70</td>
<td>−90 to −95</td>
<td>−80 to −90</td>
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<tr>
<td>Action Potential Features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude (mV)</td>
<td>60-70</td>
<td>110-120</td>
<td>70-80</td>
<td>120</td>
<td>110-120</td>
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<tr>
<td>Overshoot (mV)</td>
<td>0-10</td>
<td>30</td>
<td>5-15</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Duration (msec)</td>
<td>100-300</td>
<td>100-300</td>
<td>100-300</td>
<td>300-500</td>
<td>200-300</td>
</tr>
<tr>
<td>Vmax (V/sec)</td>
<td>1-10</td>
<td>100-200</td>
<td>5-15</td>
<td>500-700</td>
<td>100-200</td>
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<tr>
<td>Propagation velocity (m/sec)</td>
<td>&lt;0.05</td>
<td>0.3-0.4</td>
<td>0.1</td>
<td>2-3</td>
<td>0.3-0.4</td>
</tr>
<tr>
<td>Fiber diameter (µm)</td>
<td>5-10</td>
<td>10-15</td>
<td>1-10</td>
<td>100</td>
<td>10-15</td>
</tr>
</tbody>
</table>

Slowed conduction and VT in Scn5a-deficient mice

*Illustration of continuous electrical recordings from the base of the LV in response to stimuli applied to the RV septum.

Na\(^+\) Channel Isoforms in Atrioventricular Node

Inferior nodal extension

- Light blue - ring bundle myocytes
- Green - nodal myocytes
- Purple - His bundle myocytes

*Adult male Wistar rats weighing 250 to 300 g

**Circulation.** 2006;114:1360-71.
Nine different functional sodium channel α subunits have been identified.

<table>
<thead>
<tr>
<th>Channel (Gene)</th>
<th>Tissue</th>
<th>Chromosome</th>
<th>TTX sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na\textsubscript{v}1.6 (SCN8A)</td>
<td>CNS</td>
<td>15</td>
<td>TTX sensitive (IC\textsubscript{50} ~ 10 nM)</td>
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<tr>
<td>Na\textsubscript{v}1.2 (SCN2A)</td>
<td>CNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na\textsubscript{v}1.1 (SCN1A)</td>
<td>CNS</td>
<td>2</td>
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<tr>
<td>Na\textsubscript{v}1.3 (SCN3A)</td>
<td>CNS</td>
<td></td>
<td></td>
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<tr>
<td>Na\textsubscript{v}1.7 (SCN9A)</td>
<td>PNS</td>
<td></td>
<td></td>
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<td>Na\textsubscript{v}x</td>
<td></td>
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<td></td>
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<tr>
<td>Na\textsubscript{v}1.4 (SCN4A)</td>
<td>Skeletal muscle</td>
<td>11</td>
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<tr>
<td>Na\textsubscript{v}1.5 (SCN5A)</td>
<td>Heart</td>
<td></td>
<td>TTX resistant (IC\textsubscript{50} ≥ 1 μM)</td>
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<tr>
<td>Na\textsubscript{v}1.8 (SCN10A)</td>
<td>PNS</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Na\textsubscript{v}1.9 (SCN11A)</td>
<td>PNS</td>
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<td></td>
</tr>
</tbody>
</table>
Immunolabelling of **HCN4 channel** in tissue sections from SA node and AV node

- The intrinsic cycle length (CL) is $179 \pm 2.7$ ms (n=5) in SA node and $258 \pm 18.7$ ms (n=5) in AV node.
- SA node shows higher fluorescence intensity than the AV node.
- ASP, atrial septum, CT, crest terminalis, VSP, ventricular septum.


*C57BL/6J male mice weighing 20–30 g*
**Start** of inferior nodal extension (INE)

- Transitional tissue
- Densely-packed atrial muscle
- Ventricular muscle
- INE (middle)

- AM atrial myocyte
- CFB central fibrous body
- tT tendon of Todaro
- TT transitional tissue
- VM ventricular myocyte

End of INE

His bundle

Penetrating bundle

e. INE (end) – upper nodal tissue
f. INE (end) – lower nodal tissue
g. Penetrating bundle (start) – compact node
h. Penetrating bundle (start) – lower nodal tissue

**Cx43 expression by heart region**

- Neurofilament-positive nodal tissue (loosely or densely packed and Cx43-negative or -positive)
- Neurofilament-negative transitional tissue (loosely packed, Cx43-positive)
- Neurofilament-negative atrial and ventricular muscle (densely packed, Cx43-positive).

*Sections stained with Masson’s trichrome are shown on the left, and adjacent Cx43-labeled sections are shown on the right.*

• The first point was at the end of the INE via the transitional tissue.
• Secondly, the action potential entered toward the start of the INE;

• The premature S2 action potential failed to exit via the transitional tissue.
• The S2 action potential exited into the atrial muscle via the INE.
Cx43 in the human AV junction

CFB, central fibrous body; IAS, interatrial septum; ITC, inferior transitional cells; LE, leftward extension; LNB, lower nodal bundle; RE, rightward extension; VS, ventricular septum

Cx43 density in the conduction system of the AVJ

Three-dimensional reconstruction of the AVJ, conduction system.

Summary of connexin expression at the AV junction.
Serial Block Face Scanning Electron Microscopy

Advantages:
• Imaging block face rather than individual sections minimises errors, distortion and artifacts
• Large quantities of data can be collected over weeks due to system stability
• Automated process requires minimal intervention after initial system set up
Serial Block Face Scanning Electron Microscopy of the Sinoatrial Node

FIGURE 1 SEM images of rabbit sinoatrial node. A-D 2-D SEM images from the centre of the sinoatrial node. Sinoatrial node cells are spindle-shaped (A and B) and occasionally binucleated (C, arrowheads) or with a long projection (D, arrowheads) surrounded by collagen (Col), elastic (Ela) and nerve fibres (NF).

FIGURE 2 Reconstructed 3-D images of sinoatrial node cells. A and B, cells from the centre (A) and near-centre (B) of the sinoatrial node. C, morphometric profiles of sinoatrial node cells from the centre (n = 7) and near-centre (n = 13). *p < 0.05 (student’s t test).
• Conduction delay of AV node
  – Dual AV node
    • Fast pathway – Atrium → transitional tissue → end of INE → compact node → penetrating bundle
    • Slow pathway – Atrium → start of INE → INE → end of INE → compact node → penetrating bundle
  – Characteristic anatomic structure – differences in cell shape and intercellular connection
  – Differences in action potential
  – Differences in ion channel distribution
  – Differences in gap junction protein
Thank you for your attention!!!