Differential Distribution of Cardiac Ion Channel Expression as a Basis for Regional Specialization in Electrical Function

Gernot Schram, Marc Pourrier, Peter Melnyk, Stanley Nattel

Abstract—The cardiac electrical system is designed to ensure the appropriate rate and timing of contraction in all regions of the heart, which are essential for effective cardiac function. Well-controlled cardiac electrical activity depends on specialized properties of various components of the system, including the sinoatrial node, atria, atrioventricular node, His-Purkinje system, and ventricles. Cardiac electrical specialization was first recognized in the mid 1800s, but over the past 15 years, an enormous amount has been learned about how specialization is achieved by differential expression of cardiac ion channels. More recently, many aspects of the molecular basis have been revealed. Although the field is potentially vast, an appreciation of key elements is essential for any clinician or researcher wishing to understand modern cardiac electrophysiology. This article reviews the major regionally determined features of cardiac electrical function, discusses underlying ionic bases, and summarizes present knowledge of ion channel subunit distribution in relation to functional specialization. (Circ Res. 2002;90:939-950.)

Key Words: ion channels | molecular biology | conduction | cardiac arrhythmias | antiarrhythmic drugs

Cardiac function depends on the appropriate timing of contraction in various regions, as well as on appropriate heart rate. To subserve these functions, electrical activity in each region is adapted to its specialized function. Regionally specialized cardiac electrical function was recognized in the mid 1800s, when Stannius1 demonstrated that ligatures in the superior vena caval sinus region of the frog caused cardiac asystole, with the sinus continuing to beat. With the widespread application to cardiac ion channel study of patch-clamp methodologies in the 1980s and molecular biology in the 1990s, many underlying mechanisms have been unraveled. The present article reviews the major regionally determined features of cardiac electrical function and the present knowledge regarding ionic and molecular bases.

Overview of Regional Functional Specificity

Figure 1 illustrates typical regional action potential (AP) properties in the heart. The normal cardiac impulse originates in the sinoatrial node (SAN) and propagates through the atria to reach the atrioventricular node (AVN). From the AVN, electrical activity passes rapidly through the cable-like His-Purkinje system to reach the ventricles, triggering cardiac pumping action. Figure 2 shows the ionic currents involved in a schematic cardiac AP, provides standard abbreviations for currents and their corresponding subunits, and summarizes principal localization data discussed elsewhere in the present review.

Ionic and Molecular Basis of Functional Specificity

Sinoatrial Node

Cellular Electrophysiology and Function

The SAN, located in the right atrial (RA) roof between the vena cavae,2 is specialized for physiological pacemaker function. Heart rate control is achieved through autonomic regulation of SAN pacemaking. SAN APs have a relatively positive maximum diastolic potential (MDP) of $\approx -50$ mV, a small phase 0 upstroke velocity ($V_{\text{max}}, <2$ V/s),3 and prominent phase-4 depolarization maintaining SAN pacemaker dominance. The cell type changes from the typical nodal cell at the center of the SAN to the atrial cell toward the periphery.3 The longest AP durations (APDs) are in the central pacemaking zone, preventing invasion by ectopic impulses and preserving SAN dominance.4 The SAN contains both spider and spindle pacemaker cell types.5 Spider cells have a faster intrinsic rate, a less negative MDP, and a longer APD, suggesting they are primary pacemaking cells of the central node. Cholinergic and $\beta$-adrenergic stimulation slow and accelerate spontaneous SAN activity, respectively. Electrical coupling to the atrium is designed to drive the large atrial muscle mass while insulating the SAN from hyperpolarizing atrial muscle influences.6 SAN dysfunction causes bradyarrhythmias that are associated with syncope but rarely with death.7
Ionic Mechanisms

Ionic properties underlying SAN function are indicated in Figure 3. Many varieties of time-dependent currents contribute to SAN pacemaking. A key time-dependent inward current, sometimes called the pacemaker current, is the nonselective cation current ($I_{\text{f}}$). $I_{\text{f}}$ density is ≈70% greater in spider than in spindle cells. Several other currents flowing between the time of MDP and the phase-0 take off, including L-type Ca$^{2+}$ current ($I_{\text{CaL}}$), T-type Ca$^{2+}$ current ($I_{\text{CaT}}$), and the delayed rectifier K$^{+}$ current ($I_{\text{K}}$), influence pacemaking activity: inward Ca$^{2+}$ current activation and outward K$^{+}$ current deactivation contribute to diastolic depolarization. $I_{\text{CaL}}$ is particularly large in the SAN. One study found SAN pacemaker cells to lack the background K$^{+}$ current predominantly governing MDP ($I_{\text{k1}}$) and the transient outward current ($I_{\text{to}}$). The lack of $I_{\text{k1}}$ explains the positive MDP of SAN cells. A smaller rapid $I_{\text{k}}$ component ($I_{\text{k2}}$) in central SAN cells compared with peripheral cells may contribute to their more positive MDP and longer APD. A smaller sustained $I_{\text{k}}$ component may also contribute to longer APD in central SAN. $I_{\text{CaT}}$ underlies AP upstrokes in primary SAN pacemaking tissue. The Na$^{+}$ current ($I_{\text{Na}}$) may contribute to subsidiary pacemaker activity in peripheral regions, providing a backup mechanism. A sustained inward component ($I_{\text{st}}$) related to $I_{\text{CaL}}$ may also contribute to SAN depolarization, but this remains controversial.

Autonomic regulation of $I_{\text{f}}$ and $I_{\text{CaL}}$ controls heart rate. β-Adrenergic stimulation positively shifts $I_{\text{f}}$ activation volt-

**Principal Ion-channel Subunits and their Localization**

<table>
<thead>
<tr>
<th>Subunit</th>
<th>Corresponding Current</th>
<th>Primary Function</th>
<th>Demonstrated Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCN</td>
<td>$I_{\text{f}}$ (pacemaking)</td>
<td>Diastolic depolarization</td>
<td>SAN&gt;PP&gt;A-V</td>
</tr>
<tr>
<td>Kv2.1</td>
<td>$I_{\text{K1}}$</td>
<td>Resting potential, terminal repolarization</td>
<td>V$\rightarrow$AO&gt;SAN</td>
</tr>
<tr>
<td>Kv3.1/3.4</td>
<td>$I_{\text{KACR}}$</td>
<td>Mediates acetylcholine effects</td>
<td>SAN&gt;AO&gt;V</td>
</tr>
<tr>
<td>ERG</td>
<td>$I_{\text{K}}$ (n-subunit)</td>
<td>Phase-3 repolarization</td>
<td>Present in all tissues, L-A&gt;RA; 70-PF</td>
</tr>
<tr>
<td>MRP1</td>
<td>Modulates $I_{\text{K}}$</td>
<td>?</td>
<td>SAN&gt;AO&gt;AP</td>
</tr>
<tr>
<td>KvLQT1</td>
<td>$I_{\text{K}}$ (n-subunit)</td>
<td>Phase-3 repolarization</td>
<td>Abundant in A and V; 70-PF; %Dominant-negative isom in M-cellsxep or endo</td>
</tr>
<tr>
<td>minK</td>
<td>$I_{\text{Kb}}$ (n-subunit)</td>
<td>Necessary to form $I_{\text{to}}$ with KvLQT1</td>
<td>SAN&gt;AN-V</td>
</tr>
<tr>
<td>Kv4.2/4.3</td>
<td>$I_{\text{Kp}}$ (n-subunit)</td>
<td>Early (phase-1) repolarization</td>
<td>Present in A and V; Species-specific; 7-PF</td>
</tr>
<tr>
<td>Kv1.4</td>
<td>$I_{\text{Kp}}$ (n-subunit)</td>
<td>Early (phase-1) repolarization</td>
<td>Important in some species (rabbit); %Endo dominance (femt)</td>
</tr>
<tr>
<td>KChP2</td>
<td>$I_{\text{Kp}}$ (n-subunit)</td>
<td>Necessary to form $I_{\text{to}}$</td>
<td>Epigeno-in man and dog</td>
</tr>
<tr>
<td>Kv1.5/1.1</td>
<td>$I_{\text{Kw}}$</td>
<td>Phase-1-2 repolarization.</td>
<td>Atial-specific: (Kv1.5 man; Kv1.1 dog)</td>
</tr>
<tr>
<td>C4a.1.2</td>
<td>$I_{\text{CaL}}$ (n-subunit)</td>
<td>Maintenance of plateau. Electromechanical coupling. Automacity, conduction SAN, AVN</td>
<td>SAN &gt; A; 70-PF</td>
</tr>
<tr>
<td>C4a.1.3</td>
<td>$I_{\text{CaL}}$ component</td>
<td>Role in SAN function in mice.</td>
<td>%Weakly expressed in SAN, A</td>
</tr>
<tr>
<td>C4a.1.3-3.3</td>
<td>$I_{\text{CaT}}$</td>
<td>%Role in pacemaking</td>
<td>SAN&gt;AO, A; 7-PF &gt;V</td>
</tr>
<tr>
<td>Na.1.5</td>
<td>$I_{\text{Na}}$</td>
<td>Conduction A, V, PF</td>
<td>Strong in A, V, PF; Absent in compact AVN</td>
</tr>
<tr>
<td>C4a.40.43.45</td>
<td>$I_{\text{CaL}}$</td>
<td>Intracellular conduction</td>
<td>Cx44 strong in A, V, PF; Absent in central SAN, AVN, Cx43 in peripheral SAN, central AVN, PF</td>
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**Figure 2.** Principal cardiac ion channel subunits, corresponding currents, and localization. Inset shows schematic diagram of cardiac AP and currents involved in different phases. Outward currents correspond to upward arrows; inward currents correspond to downward arrows.
Age dependence, accelerating diastolic depolarization,9,16 Adrenergically induced increases in \( I_{\text{CaL}} \) conductance also enhance SAN phase-4 terminal depolarization.9,10 Acetylcholine slows SAN activity by reducing \( I_{\text{f}} \), activating the acetylcholine-sensitive K\(^+\) current (\( I_{\text{KACH}} \)) and reducing \( I_{\text{CaL}} \).9 The potency of acetylcholine for \( I_{\text{f}} \) inhibition is greater than that for \( I_{\text{KACH}} \) activation,17 which in turn is greater than that for \( I_{\text{CaL}} \) inhibition.9 \( I_{\text{f}} \) is also autonomically regulated.18

**Molecular Basis**

Hyperpolarization-activated cation channel (HCN)1-HCN4 cDNAs encode \( I_{\text{f}} \)-like currents.19–22 HCN transcripts are 25 times more abundant in the SAN than in Purkinje cells (PCs) and \( \approx 140 \) times more abundant than in ventricular myocardium.20 HCN1 protein and message and HCN4 transcripts are abundant in rabbit SAN, whereas HCN2 protein expression is weak, and HCN3 mRNA is absent.19–21 In the mouse, SAN HCN4 transcripts are abundant, HCN2 levels are moderate, and HCN1 levels are low.22 HCN1 and HCN2 coassemble to form functionally distinct channels.23 The minK-related protein, MiRP1, increases the density and activation rate of \( I_{\text{f}} \), resulting from HCN expression.24 MiRP1 mRNA is highly expressed in rabbit SAN, likely contributing to SAN pacemaker function.24

Expression of Kir2.1, the predominant cardiac \( I_{\text{K1}} \) subunit, is very limited in ferret SAN, which is consistent with the virtual absence of \( I_{\text{K1}} \).25 \( I_{\text{KACH}} \) is formed by complexes containing Kir3.1 and Kir3.4 subunits.26 Kir3.1 protein is present in rat, ferret, and guinea pig SAN.27 Kir3.1 and \( m_3 \)-receptor proteins colocalize.27 Kir3.4 protein is present in rat SAN.27

Four subunits are believed to contribute to \( I_{\text{K1}} \): the ether-a-go-go–related (ERG) and MiRP1 subunits (thought to be \( \alpha \) and \( \beta \) subunits of \( I_{\text{f}} \), respectively)28 and KvLQT1 and minK (\( \alpha \) and \( \beta \) subunits of \( I_{\text{K1}} \), respectively).29 although the role of MiRP1 remains controversial.30 MinK transcripts are more abundant in the SAN than in the atrium or ventricle.25 ERG protein and transcript are correlated with the presence of \( I_{\text{K1}} \) in ferret13 and rabbit29 SAN.

Voltage-activated Ca\(^{2+}\) channel (Ca\(_{\text{L}}\).3.1 and Ca\(_{\text{L}}\).3.2 encode \( I_{\text{CaL}} \) \( \alpha \) subunits.33,34 Ca\(_{\text{L}}\).3.1 mRNA expression is 30-fold greater in mouse SAN than in mouse atrium.35 Ca\(_{\text{L}}\).3.2 expression is lower than Ca\(_{\text{L}}\).3.1 expression, but it is also greater in the SAN.35 Ca\(_{\text{L}}\).1.2 and Ca\(_{\text{L}}\).1.3 are \( I_{\text{Ca}} \) \( \alpha \) subunits. Ca\(_{\text{L}}\).1.3 mRNA expression is low in mouse SAN and atrium,35 but Ca\(_{\text{L}}\).1.3 knockout creates marked SAN dysfunction.36 Ca\(_{\text{L}}\).1.2 transcripts are more numerous and are more strongly expressed in the SAN than in the atrium.35 Subunits \( \beta \) and \( \alpha_\delta \) modulate the density, kinetics, and activation/inactivation of \( I_{\text{CaL}} \).37 Little is known about their cardiac localization.

Gap-junctional hemichannel connexin (Cx) proteins are the basis of intercellular electrical coupling.38 The SAN is shielded against hyperpolarizing atrial influences by compartmentalization of Cx expression.6 Many studies report that Cx43, the major cardiac Cx, is absent in the central SAN.6,27,39,40 Cx43 has been detected in the SAN of rabbits,41 hamsters,42 and dogs.43 Cx45 and Cx40 are expressed in the SAN of rabbit and human hearts.6,44 Cx46 is present in rabbit SAN.40 In canine SAN, 55% of the cells express Cx40 alone; 35% express Cx43, Cx45, and Cx40; and 10% show no Cx.34 Cells expressing all 3 connexins are located in bundles abutting atrial tissue, whereas Cx40-expressing cells are located in the central SAN.34 Myocytes coexpressing Cx40, Cx43, and Cx45 extend from the SAN into the atrium, transmitting pacemaker impulses that drive the atrium.43,45

**Atrium**

**Cellular Electrophysiology and Function**

The MDP in multicellular atrial preparations is \( \approx 80 \) mV.46,47 Isolated atrial-myocyte MDP averages \( \approx 70 \) mV.48,49 Atrial APs have MDPs \( \approx 5 \) to 10 mV less negative than ventricular myocytes, exhibit slower phase-3 repolarization, and have little or no spontaneous phase-4 depolarization.

Spatial atrial AP/ADP heterogeneity occurs within and between atrial regions50–53 and plays a role in atrial reentrant arrhythmias.51 RA APD decreases progressively from the cribriformis to the pectinate muscles,51 helping to “stream” the impulses from the SAN toward the AVN.54 Rapid conduction follows fiber orientation in thicker bundles.55 The APD and effective refractory period (ERP) are shorter in the left atrial (LA) free wall than in the RA.49 In guinea pigs, cells from LA sleeves around proximal pulmo-
nary veins have APs similar to those in atrial myocytes, whereas more distally located cells have less negative MDP, shorter APD, and slow pacemaker activity.

Animal models and clinical studies suggest an important role of the LA in atrial fibrillation. This may partly be due to accelerated LA repolarization, which shortens ERPs, favoring reentry. LA pulmonary vein activity also triggers atrial fibrillation. In guinea pigs, pulmonary vein cells generate atrial tachycardias that are due to digitalis-induced triggered activity. Parasympathetic stimulation shortens atrial APD in a spatially heterogeneous fashion, producing important proarrhythmic effects.

**Ionic Mechanisms**

The ionic mechanisms of atrial cell APs are summarized in Figure 4. A role for \( I_{f} \) in atrial ectopy has been suggested, but atrial tachycardia--induced ionic remodeling has been questioned because of limited activation at atrial MDP.

Atrial cells have large inward \( I_{f} \) providing energy for rapid conduction.

Atrial \( I_{K} \) is 6- to 10-fold smaller than ventricular \( I_{K} \), explaining the less negative atrial MDP and slower phase-3 repolarization. Ultrarapid delayed rectifier current (\( I_{Kur} \)), activating two orders of magnitude faster than \( I_{Kr} \), has been described in rat, mouse, human, and canine atria. In humans and dogs, \( I_{Kur} \) is present in atria but not in ventricles. Atrial \( I_{K} \) includes both \( I_{Kur} \) and the slow component, \( I_{Kr} \). Unlike normal ventricular myocytes, in which \( I_{CaT} \) is lacking in the absence of cardiac hypertrophy, \( I_{CaT} \) is readily detectable in atrial myocytes and may be important in atrial tachycardia–induced ionic remodeling.

Atrial tachyarrhythmias and heart failure produce discrete atrial ionic remodeling, which is important in arrhythmogenesis. A recent study suggests that atrial tachycardia causes remodeling and afterdepolarizations in pulmonary vein myocytes. A number of discrepancies make that study difficult to interpret; these discrepancies include an \( I_{f} \) reversal potential of −40 mV in cells with a resting potential of −65 mV, the simultaneous measurement of inward and outward currents with similar kinetics at the same test potentials with no attempt to isolate components, and the generation of 25-mV delayed afterdepolarizations by transient inward currents <10 pA.

Myocytes from different RA regions show discrete ionic current distributions that explain their AP properties. LA free-wall myocytes have larger \( I_{K} \) compared with RA, accounting for their shorter APDs and ERPs. LA \( I_{Kur} \) density is 6 times greater in the atrium than in the ventricle.

**Molecular Basis**

HCN2 and HCN4 are expressed in the atrium. HCN4 message levels are much lower in the atrium than in the SAN.

Kir2.1 is the most abundant Kir2-family (\( I_{Ks} \) subunit mRNA in the atrium and ventricle and is equally expressed in each. Kir2.3 transcripts are more concentrated in human atrium than ventricle, and Kir2.2 transcripts are equal and sparse in both. Kir2.3 subunit mRNA expression does not account for atrioventricular differences. Kir2.1 protein expression is 80% greater in the ventricle than in the atrium, whereas Kir2.3 protein expression is 228% greater in the atrium. Kir2.3 protein localizes to transverse tubules of most atrial but few ventricular cells, whereas the converse is true of Kir2.1. The role of these atrioventricular differences in Kir2 protein expression in the much weaker atrial \( I_{K} \) is uncertain.

Kir3.1 mRNAs are expressed strongly in rat atria but not ventricles, and Kir3.1 and Kir3.4 proteins are abundant in the atrium and sparse in the ventricle, consistent with predominantly atrial \( I_{Ks} \) expression. Recent work suggests that homomeric Kir3.4 channels may also contribute to atrial \( I_{Ks} \). The principal subunits thought to encode \( I_{Ks} \) include Kv1.4, Kv4.2, and Kv4.3. Kv4.2 contributes to rat atrial \( I_{Ks} \), localizing to the sarcolemma and T tubules. Kv4.1 transcript expression is stronger in rat atrium than ventricle, but Kv4.1 protein is almost undetectable in both. In rabbit atrium, Kv1.4 is a major contributor to \( I_{Ks} \) whereas in human atrium, \( I_{Ks} \) is encoded entirely by Kv4.3.
The molecular basis of atrial $I_{\text{Kr}}$ varies widely among species. $98$ Kv1.2 and Kv1.5 contribute to rat atrial $I_{\text{Kr}}$. $93$ Human atrial $I_{\text{Kr}}$ is encoded by Kv1.5, with no corresponding component in the ventricle. $99$ Kv3.1 is the molecular basis of canine atrial $I_{\text{Kr}}$, and like the corresponding current, it is absent in the ventricle. $76$

KvLQT1 transcripts are abundant in ferret RA. $100$ MinK is less abundant in the atrium than in the SAN. $100$ ERG mRNA is abundantly expressed in the atrium, as is the longer (ERG*) variant, with larger expression in the ventricle versus atrium in humans and larger expression in the atrium versus ventricle in rats. $101$

ERG protein levels in dogs are larger in the LA than in the RA, consistent with a larger LA $I_{\text{Kr}}$. $49$ No information is available about the molecular basis of intra-atrial regional differences in $I_{\text{Kr}}$ and $I_{\text{CaL}}$. $52$ Cardiomyocytes in pulmonary veins contain Kir2.1 subunits and show $I_{\text{Kir}}$-like currents, $102$ but otherwise, little is known about their molecular electrophysiology.

Ca,3.1 and Ca,3.2 transcripts are found in mouse atrium, $35$ consistent with the atrial presence of $I_{\text{CaL}}$. Ca,1.2 transcripts are abundant in the atria, and their downregulation is believed to be central to atrial electrical remodeling. $103,104$ The Na* channel $\alpha$ subunit, Na,1.5, is abundantly expressed in atrial myocytes, on the atrial surface, and in T-tubular membranes and intercalated disks, consistent with large $I_{\text{Na}}$. $105$

Cx43 protein is present on bovine, guinea pig, and human atrial myocytes, $106-108$ with a distinct transitional zone containing interdigitating Cx43-expressing atrial and Cx43-lacking nodal cells at the periphery of the SAN. $45,106,108$ Canine and rabbit RA gap junctions contain mainly Cx40 and Cx43 and less Cx45. $39,109$ Cx40 expression in the atrium is much stronger than in the ventricle (where it is virtually undetectable) in humans, rabbits, guinea pigs, and mice. $107,109-111$ Cx40 is more abundant in human RA than LA. $107$

### Atrioventricular Node

**Cellular Electrophysiology and Function**

The primary function of the AVN is to govern the ventricular response to supraventricular activation. AVN cells have low excitability and postrepolarization refractoriness, $112$ which limit the maximum number of impulses that can traverse to the ventricles and prevent dangerously rapid ventricular rates in response to supraventricular tachyarrhythmias.

The AVN has a complex 3D structure. APs from intact AVN have slow upstrokes and small amplitudes. $114$ Within the compact AVN, MDPs are $\approx64$ mV, phase-4 depolarization results in takeoff potentials of $\approx60$ mV, and $V_{\text{max}}$ is $<20$ V/s. $115$ Cell types include N cells in the compact node and NH cells at the junction with the His bundle. $113$ A modern classification divides the AVN into a transitional cell area, compact node, posterior nodal extension, and lower nodal cell bundle. $116$

Ovoid and rod-shaped cells have been isolated from the compact AVN. $117$ Ovoid cells have N- or NH-like APs showing postrepolarization refractoriness and no AP abbreviation with increased frequency, less negative MDPs, faster diastolic-depolarization, and smaller $V_{\text{max}}$ than those in rod-shaped cells. Rod-shaped cells display APs intermediate...

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**Figure 5.** Basis of AVN cell AP properties. AP is reproduced from Munk AA, Adjemian RA, Zhao J, Ogbaghebriel A, Shrier A. Electrophysiological properties of morphologically distinct cells isolated from the rat atrioventricular node. J Physiol. 1996;493:801–818, by permission of The Physiological Society ©1996.

The ionic basis of AVN properties is illustrated in Figure 5. $I_{\text{f}}$ is present in 95% of ovoid cells versus $\approx10\%$ of rod-shaped cells, and $I_{\text{f}}$ density is $\approx25$-fold larger in ovoid cells, which is consistent with the much greater ovoid cell pacemaker activity. $117$ $I_{\text{Kr}}$ and $I_{\text{Na}}$ are present in few ovoid cells but in almost all rod-shaped cells. $117$ $I_{\text{CaL}}$ underlies the compact AVN AP upstroke. $123$ 4-Aminopyridine inhibits spontaneous AVN APs, which is consistent with a role for $I_{\text{Kr}}$ in AVN pacemaking. $124$ $I_{\text{Na}}$ elimination in transgenic mice causes atrioventricular block. $125$

$I_{\text{f}}$ deactivates faster in AVN than in ventricular myocytes. $126$ Contrary to the SAN, where both $I_{\text{Kr}}$ and $I_{\text{CaL}}$ are important, $I_{\text{Kr}}$ predominates in the AVN. $127$ $I_{\text{Kr}}$ activation contributes to AVN repolarization and deactivation to diastolic depolarization. $123$ There is little $I_{\text{K1}}$ in the AVN, consistent with its positive MDP.

**Molecular Basis**

Data regarding ion channel subunit distribution in the AVN are limited. As opposed to transitional or lower nodal cells, midnodal cells of the rabbit AVN display little or no Na+ channel $\alpha$ subunit or Cx43 protein. $128$ Cx43 expression is sparse or absent in the AVN. $129-132$ Low-level Cx43 expression colocalizes with Cx40 in the rat. $132$ Targeted disruption...
of Cx40-subunit expression impairs atrioventricular conduction in the mouse,\textsuperscript{133–135} although much of the delay is attributable to slowing in the ventricular conduction system.\textsuperscript{136} Cx45 is strongly expressed in the rodent AVN and conducting system.\textsuperscript{137}

**His-Purkinje System**

**Cellular Electrophysiology and Function**

PCs forming the bundles of His and the Purkinje system are specialized for rapid conduction. PC MDP is 5 to 10 mV more negative (averaging \( \approx -90 \) mV) than is working ventricular MDP.\textsuperscript{138,139} \( V_{\text{max}} \) is also greater in PCs (\( \approx 400 \) to 800 V/s) than in the ventricle (150 to 300 V/s), and the PC plateau voltage is lower.\textsuperscript{138,139} APD is more prolonged in PCs than in ventricular muscle at slow rates.\textsuperscript{140,141} PCs show prominent phase-4 depolarization, providing ventricular escape pacemakers.\textsuperscript{142} PCs preferentially generate drug-induced early afterdepolarizations that excite adjacent ventricular muscle,\textsuperscript{151} likely explaining endocardial early afterdepolarizations that trigger torsade de pointes arrhythmias.\textsuperscript{143,144}

**Ionic Mechanisms**

Multicellular Purkinje fiber preparations were used for classic voltage-clamp studies because of favorable geometry; however, because of the difficulty of isolating PCs, much less work has been done recently. Ionic bases for PC AP properties are illustrated in Figure 6. Both \( I_{\text{Ca,L}} \) and \( I_{\text{Ca,T}} \) are present in PCs, with \( I_{\text{Ca,L}} \) being quite substantial.\textsuperscript{145,146} PCs have a smaller \( I_{\text{Ca,L}} \) than ventricular myocytes, consistent with their less positive plateau.\textsuperscript{147} \( I_{\text{Ca,T}} \) inhibition does not affect Purkinje fiber automaticity, suggesting that \( I_{\text{Ca,T}} \) may not be important for PC pacemaking.\textsuperscript{148}

Two studies showed smaller \( I_{\text{K1}} \) in PCs than in ventricular muscle,\textsuperscript{147,149} whereas one study showed no significant differences.\textsuperscript{150} \( I_{\text{K1}} \) in human\textsuperscript{150} and canine\textsuperscript{151} PCs displays striking differences compared with ventricular myocytes, including sensitivity to 10 mmol/L tetraethylammonium, \( \approx 9 \)-fold greater sensitivity to 4-aminopyridine, and slower reactivation. PC \( I_{\text{K1}} \) resembles ventricular and atrial \( I_{\text{K1}} \).\textsuperscript{152} \( I_{\text{K1}} \) is observed in human PCs, consistent with their pacemaker activity.\textsuperscript{150} Slowly inactivating \( I_{\text{K1}} \) may contribute to maintaining PC APD, especially at slow rates.\textsuperscript{153} Downregulation of \( I_{\text{K1}} \) and \( I_{\text{K1}} \) in PCs of dogs with congestive heart failure enhances their sensitivity to \( I_{\text{K1}} \), blocker–induced APD prolongation, possibly explaining the increased risk of drug-induced long-QT syndrome in patients with congestive heart failure.\textsuperscript{154}

**Molecular Basis**

HCN1 and HCN4 transcripts are expressed in rat and rabbit Purkinje fibers.\textsuperscript{20} HCN expression in PCs is lower than that in the SAN but higher than that in ventricles.\textsuperscript{20}

Canine Purkinje fibers do not significantly express Kv4.2 or Kv1.4 mRNA, and Kv4.3 mRNA levels in PCs are similar to those in the midmyocardium.\textsuperscript{155} \( K^+ \) channel interacting protein (KChIP)2 mRNA is denser in myocardium than in PCs, whereas Kv3.4 is more concentrated in PCs,\textsuperscript{155} compatible with their tetraethylammonium-sensitive \( I_{\text{K1}} \).\textsuperscript{152} ERG and KvLQT1 mRNA levels are lower in PCs,\textsuperscript{155} suggesting that smaller \( I_{\text{K1}} \) may contribute to their longer APD. Ca\textsubscript{1.2} mRNA levels are lower in PCs,\textsuperscript{155} consistent with their smaller \( I_{\text{Ca,L}} \).\textsuperscript{147} Ca3.1, Ca3.2, and Ca3.3 expression is much greater in PCs than in the ventricle,\textsuperscript{155} compatible with their large \( I_{\text{Ca,L}} \).\textsuperscript{145,146}

\( \text{Cx40} \) mRNA is 3 to 5 times more abundant in PCs than in the ventricle.\textsuperscript{39,44,156} Cx40 colocalizes with Cx43 in the rat cardiac conducting system.\textsuperscript{132} Cx45 in mouse and rat hearts is found only in the His-Purkinje system.\textsuperscript{137} The extensive expression of Cx in Purkinje tissue may be crucial for very rapid conduction.

**Ventricular Muscle**

**Cellular Electrophysiology and Function**

MDPs of ventricular myocytes are \( \approx -85 \) mV.\textsuperscript{138,139,158} The plateau is relatively positive, at \( \approx 10 \) to 20 mV, and phase-3 repolarization is rapid. As in working atrial muscle, there is no significant phase-4 depolarization or automaticity.

Regional ventricular AP heterogeneity is well established. Compared with endocardium, epicardial APs show a smaller overshoot, a more prominent phase 1 followed by a notch (spike and dome), and a briefer APD, but M-cell APs in the right ventricle (RV) compared with the left ventricle (LV) have a smaller upstroke, a deeper notch, and a shorter duration.\textsuperscript{162} In the rat, APD is shortest at the apex and longest in the septum, with intermediate values in the free wall.\textsuperscript{163} Transmural ERP heterogeneity caused by differential M-cell APD prolongation may contribute to torsade de pointes by promoting transmural reentry,\textsuperscript{164} particularly in the presence of hypokalemia, slow heart rates, and APD-prolonging drugs.\textsuperscript{165}

**Ionic Mechanisms**

The information available about the ionic bases of transmural AP heterogeneity in the ventricles is summarized in Figure 7. \( I_{\text{wo}} \) differences between epicardium and endocardium were originally inferred from phase-1 repolarization properties.\textsuperscript{159} \( I_{\text{wo}} \) is larger in epicardium than endocardium for dogs, cats,
endocardial expression of Kv1.4 versus epicardial predominance of Kv4.2 and Kv4.3.186 Kv4.3 underlies \( I_{Ks} \) in dog and human hearts.187,188 Kv4.2 mRNA is not detectable in canine187 or human189 ventricle. Kv4.2 is thought to encode the fast component and Kv1.4 is thought to encode the slow component of \( I_{Ks} \) in rodents.190 Kv4.1 mRNA expression is very low, suggesting little importance for native cardiac \( I_{Ks} \).195

KChIP2 substantially increases functional expression and modifies inactivation of Kv4 subunits.191 KChIP2 expression is greater in the epicardium than in the endocardium, consistent with the transmural \( I_{Ks} \) gradient, whereas Kv4.3 is uniformly expressed across the wall.192 KChIP2 knockout virtually eliminates \( I_{Ks} \).193 KChAP may be a chaperone for Kv channels that form \( I_{Ks} \).194

Kv1.5 has been observed at the intercalated disk of human ventricular and atrial myocytes, but longitudinal membrane staining is seen only in the atrium,195 perhaps accounting for atrium-specific expression of the corresponding current.75,99 Rat Kv2.1 is more abundant in the ventricle than in the atrium.93 Kv2.1 may encode rat ventricular \( I_{Ks} \), but there is poor correlation between Kv2.1 expression and \( I_{Ks} \) density in rat ventricle.196

Human minK mRNA levels are not significantly different among epicardial, midmyocardial, and endocardial tissues.197 However, a dominant negative KvLQT1 splice variant (isoform 2) is more strongly expressed in the midmyocardium, potentially accounting for lower \( I_{Ks} \) in M cells.197 In the ferret, ERG protein expression is stronger in the epicardium.31 ERG mRNA is 1.5-fold more abundant than Kv4.3 in canine RV and is the most prevalent K+ channel species in the heart,32 consistent with its prominent role in repolarization. MiRP1 is expressed sparsely in rabbit ventricle.24 Along with recent studies showing limited effects of MiRP1 coexpression on ERG currents,30 this observation raises questions about the role of MiRP1 in ventricular \( I_{Ks} \).

Ca.1,2 and \( I_{Ca,1} \) \( \beta \) and \( \alpha_{F} / \beta \) subunits are present in the human septum and LV.198 Na.1.1 and \( \beta \) and \( \beta_{F} \) subunits are expressed along the Z lines in adult rat cardiac myocytes.199 \( \beta_{F} \) subunits modulate \( I_{Ks} \), but \( \beta_{F} \)-subunit function may be limited to cell adhesion.199 As in the atrium, in the ventricles, Na.1.5 is the principal Na+ channel \( \alpha_{F} \) subunit found on membranes and the T-tubular system and at the intercalated disk region.105

Cx43 is the predominant Cx in the ventricles.107,111,156 Heterozygous knockout of Cx43 slowed ventricular conduction in adult mice, with minimal effects on the atrium, as reported in one study,111 but did not affect conduction in mouse embryos in another.200 Homozygote Cx43 knockouts had severe impairment of ventricular conduction, consistent with a critical role in ventricular conduction that can be compensated in the heterozygote.200

**Conclusions**

A tremendous amount has been learned over the last 10 to 15 years regarding the ionic and molecular basis of cardiac regional electrical specialization. Nevertheless, many aspects remain unexplained. The molecular biology of ion channel expression in the AVN and Purkinje fibers remains largely unexplored. The basis of intra-atrial and intraventricular
regional variations in ion channel function remains poorly understood, and the distribution of ion channel subunits in specific cellular subtypes in complex regions such as the SAN and AVN remains largely unknown. Species differences in ion channel distribution are incompletely understood and complicate extrapolations of experimental findings to humans. The effects of disease states on regional ion channel function are virtually unknown. Targeted modulation of regional ion channel function by genetic engineering approaches may open up entirely new therapeutic vistas, and its feasibility has been demonstrated.203

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