HHS Public Access

Author manuscript

Compr Physiol. Author manuscript; available in PMC 2016 July 01.

Published in final edited form as:

Compr Physiol. 2015 July 1; 5(3): 1423–1464. doi:10.1002/cphy.c140069.

Ion Channels in the Heart

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Abstract

Optimal cardiac function depends on proper timing of excitation and contraction in various regions of the heart, as well as on appropriate heart rate. This is accomplished via specialized electrical properties of various components of the system, including the sinoatrial node, atria, atrioventricular node, His-Purkinje system, and ventricles. Here we review the major regionally-determined electrical properties of these cardiac regions and present the available data regarding the molecular and ionic bases of regional cardiac function and dysfunction. Understanding these differences is of fundamental importance for the investigation of arrhythmia mechanisms and pharmacotherapy.

Introduction

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 coordinated cardiac pumping action. The various cardiac regions are characterized by specific action potential (AP) morphology and duration, which result from regionally distinct collections of ionic currents. The molecular and ionic bases of regionally defined electrophysiology are reviewed here, along with region-specific heart disease-induced remodeling and its functional consequences.

In this review, the molecular and ionic bases of regionally defined electrophysiology are summarized, along with region-specific heart disease-induced remodeling and its functional consequences. The review is organized functionally following the propagation of the AP (SAN, atrium, AVN, His-Purkinje system, ventricles). For each major region of the heart, function, ionic mechanisms, and molecular bases are first discussed (Figure 1C). Heterogeneity within each region is then highlighted, with particular emphasis on species differences and atrioventricular differences discussed in the ventricular section. Finally, a discussion of both inherited and acquired cardiac disease is covered, including what is currently known about pathology-induced remodeling of ion channels. Both experimental and computational findings are discussed throughout this review. For a more detailed discussion of methodologies pertaining to these findings, the reader is referred to the following excellent methodological reviews (453).

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Sinoatrial Node

Function

The SAN is the primary pacemaker in the normally functioning heart and is an electrophysiologically and anatomically heterogeneous and complex structure. The human SAN is a crescent-shaped, intramural structure with its head located subepicardially at the junction of the right atrium and the superior vena cava and its tail extending 10 to 20 mm along the crista terminalis (Figure 1A and Figure 2A). Although once thought to be a relatively compact and discrete structure, recent evidence has revealed a more diffuse elaborate structure, with an extensive ‘paranodal area’ identified in humans located within the crista terminalis and comprised of loosely packed nodal and atrial myocytes (101).

Source-sink relationships are critical to proper functioning of the SAN and exactly how the depolarizing ‘source’ current generated by the SAN drives depolarization and activation of the surrounding atrial tissue (current ‘sink’) remains unclear. It has been proposed that the SAN is not functionally continuous with the atrial myocardium, but rather areas of functional or anatomical conduction block exist, creating discrete sites at which SAN activation can exit the node to excite the atrial myocardium (435). Electrical and optical mapping studies in rabbit, canine, and human SAN have confirmed the presence of areas of functional conduction block and discrete exit pathways (62, 167, 168). Such an arrangement would allow for electrical insulation of the SAN from the surrounding atrial myocardium and hence a reduction in the source-sink mismatch. Despite the convincing functional data, detailed histological studies in the human heart have failed to demonstrate evidence for an insulating or fibrous sheath surrounding the SAN (323, 419), suggesting that this may be a functional rather than anatomical phenomenon. Indeed, as discussed below, differential expression of ion channels and gap junctions plays an important role in the emergent function of the SAN.

SAN APs are markedly different from those of the working atrial myocardium, with diastolic Phase 4 depolarization (also called the ‘pacemaker potential’) (77) as the hallmark (Figure 2C). When diastolic depolarization reaches a threshold potential, an AP is triggered. The rate of diastolic depolarization determines how quickly the threshold potential is reached, hence providing heart rate modulation. Other key features of the SAN AP are a relatively depolarized (less negative) diastolic membrane potential, E_m, (−60 to −70 mV) and a slow upstroke (<10 V/s), mainly driven by L-type Ca^{2+} current (I_{CaL}).

Ionic Mechanisms and Molecular Bases

Since the discovery of the SAN by Keith and Flack over a century ago (258), the underlying mechanisms of the pacemaker potential and diastolic depolarization have remained an area of intense investigation. Currently, two main hypotheses have emerged, the first positing that the ‘voltage clock’, predominantly comprised of the ‘funny current’ (I_f), is a major contributor to the pacemaker potential (141), whereas the second proposes the importance of the ‘Ca^{2+} clock’ in diastolic depolarization (276, 317). Although a plethora of experimental studies have demonstrated the existence and physiological relevance of each clock system, there is currently no consensus as to the importance or predominance of either clock. Here,

we will not review the detailed evidence for or against either hypothesis (see *Point/Counterpoint* by Lakatta and DiFrancesco (275)), but rather will provide an overview of each system and the mechanisms by which each clock system, both alone and in combination, contribute to the pacemaker potential. Indeed, the current paradigm suggests the 2 clocks function in concert in a 'coupled clock' system (411).

Voltage Clock—The best-known SAN ionic current is I_f, the 'funny current', which is an inward current carried by Na^+ and K^+ and is activated at hyperpolarized E_m (139, 140). The hyperpolarization-activated cyclic-nucleotide gated (HCN) channel is responsible for I_f, with HCN1 and HCN4 the predominant human isoforms (101). I_f is activated during Phase 4 of the AP and a reduction in I_f with either CsCl or ivabradine leads to a reduction in heart rate due to a decrease in the slope of the pacemaker potential (Figure 2D)(65, 85, 357). Conversely, β-adrenergic receptor stimulation leads to an increase in I_f and heart rate due to cAMP (produced in response to β-adrenergic receptor stimulation) binding to the HCN channel via a cytoplasmic cyclic nucleotide binding domain (530). On the other hand, it has been shown that transgenic mice lacking HCN4 have preserved response to β-adrenergic stimulation (36).

Although I_f provides an inward depolarizing current that contributes to diastolic depolarization, working in concert with I_f in the SAN is a reduction in outward K^+ currents. The SAN has no Kir2.1 channels (101), resulting in a lack of inward rectifier K^+ current (I_{K1}), which acts to stabilize the resting E_m in the normal working atrial and ventricular myocardium. In fact, knocking out Kir2.1 in the ventricles results in pacemaking activity (328). Additionally, the delayed rectifier K^+ currents (I_{Kr} and I_{Ks}), which are responsible for repolarization of the SAN AP, decay following repolarization, allowing I_f and other inward currents to depolarize the cell. Indeed, this decay in K^+ currents was once thought to be the major mechanism responsible for the pacemaker potential (487).

SAN myocytes express both L-type and T-type Ca^{2+} channels. The T-type Ca^{2+} channels Cav3.1-Cav3.3 are significantly more abundant in the SAN than in the working myocardium (101) and the T-type Ca^{2+} current (I_{CaT}) contributes to the final phase of diastolic depolarization (208). I_{CaL} in the SAN is the predominant current responsible for the SAN AP upstroke (in central nodal cells (265), see below) and is dependent upon Cav1.3 (and perhaps to a lesser extent Cav1.2), while in the working myocardium I_{CaL} is exclusively carried by Cav1.2 (477). Cav1.3 has a more negative threshold potential compared to Cav1.2, thus it activates earlier during diastolic depolarization which may be advantageous in pacemaker cells which rely upon I_{CaL} for the AP upstroke (318).

The fast inward Na^+ current (I_{Na}, carried by Nav1.5), normally responsible for the AP upstroke in the working atrial and ventricular myocardium, is present in the periphery of the SAN but is absent from central SAN cells (Figure 2C) (101, 477). This explains the slow I_{CaL}-dependent upstrokes of the central SAN cells (265). I_{Na} in the SAN periphery contributes to a faster AP upstroke in these regions and is discussed in more detail below.

Ca^{2+} Clock—In addition to the membrane currents discussed, intracellular Ca^{2+} handling also contributes to pacemaking in the SAN. Lakatta and colleagues have shown that Ca^{2+} is

spontaneously released from the sarcoplasmic reticulum (SR) late during the pacemaker potential (64, 276), and is not triggered by I_{CaT} as previously proposed (593). Ca^{2+} released from the SR (via the ryanodine receptor [RyR]) instantaneously triggers Ca^{2+} extrusion from the cytosol by the Na^{+}-Ca^{2+} exchanger (NCX). NCX exchanges 3 Na^{+} ions for each Ca^{2+} ion, thus generating a net inward current (I_{NCX}) that is thought to contribute to the final phase of diastolic depolarization (63). In agreement with this interpretation, slowing of diastolic depolarization and heart rate by block of SR Ca^{2+} release with ryanodine have been reported (Figure 2E) (64). The mechanism that permits SAN, but not ventricular myocytes to generate rhythmic diastolic Ca^{2+} releases under basal conditions has not been fully resolved, but may owe to higher cAMP and basal cAMP-mediated, PKA-dependent phosphorylation of phospholamban (PLB) in these cells compared with other cardiac cell types (519). Basal PKA phosphorylation is required for maintaining pacemaker activity, and stimulation of the β-adrenergic receptors with isoproterenol increases the frequency of diastolic SR Ca^{2+} releases (519). Furthermore, isoproterenol fails to increase the heart rate *in vivo* in the presence of ryanodine (519). The Anderson group has confirmed the importance of the Ca^{2+} clock in regulation of SAN automaticity, and showed that CaMKII inhibition (using transgenic mice or peptides) reduces the heart rate during β-adrenergic challenge (but not in basal conditions) (562).

Several lines of experimental and computational evidence support the role of the Ca^{2+} clock and the ‘coupled clock’ system in contributing to the pacemaker potential (578). Notably, membrane currents play a fundamental role not only in AP generation, but also in resetting the Ca^{2+} clock via Ca^{2+}-induced Ca^{2+} release, i.e., allowing the refilling of the SR with Ca^{2+}, which is important to ensure that the threshold of SR Ca^{2+} load needed for the next spontaneous Ca^{2+} release is reached.

SAN Heterogeneity: Ion Channel and Gap Junction Distribution

The SAN has a complex 3-dimensional architecture with central and peripheral or ‘paranodal’ components made up of distinct ion channel and gap junction expression profiles. Central and peripheral cells have progressively different AP characteristics and conduction properties (Figure 2C). Experimental and computational studies have demonstrated that SAN heterogeneity is necessary to maintain normal pacemaking activity and impulse conduction.

Figure 2C shows typical central and peripheral SAN APs. Boyett and colleagues have suggested that AP properties show a gradual transition from the central to peripheral SAN, termed the ‘gradient’ model (76), whereas others have suggested that only a few distinct types of nodal cells exist and they are interspersed with each other and with atrial cells in a ‘mosaic model’ (515). Regardless of the proposed model of cell heterogeneity, it is well documented that central SAN APs have a slow upstroke velocity, relatively long AP duration (APD), and less negative maximum diastolic E_m compared to peripheral SAN and atrial APs (265). These AP changes are accompanied by differential expression of several ion channels, with the peripheral SAN cells often having an intermediate expression profile between the central SAN and atrial myocytes.

One of the main differences between central and peripheral SAN myocytes is the differential expression of Nav1.5, with little or no expression in the central SAN (101, 477) and no measurable I_{Na}. Nav1.5 expression increases from the central to peripheral SAN and increases even more in the working atrial myocardium, resulting in increasing amounts of I_{Na}, which contributes to the progressive increase in upstroke velocity of APs from central to peripheral SAN to atrial myocardium (226). Other Na^+ channel isoforms have also been found in the central and peripheral SAN, including Nav1.2 and Nav1.4 in the human SAN (101). However, at the mRNA level, their expression levels were >100-fold lower than Nav1.5. Interestingly, in the mouse neuronal Na channels (TTX-sensitive, Nav1.1) are expressed throughout the SAN and block of these channels with nM concentrations of TTX results in a significant slowing of pacemaking without an impact on SAN conduction (281). The functional role of neuronal Na channels in contributing to pacemaking and conduction in the human SAN remains to be determined.

In both human and rabbit SAN, isoform switching from predominantly Cav1.2 in the atria to Cav1.3 in the central SAN has been found, with the peripheral SAN having intermediate expression of the two isoforms in the rabbit (477) and an expression profile similar to the atria in the human (101). This isoform switch likely reflects the different roles of I_{CaL} in the central SAN, where it contributes to diastolic depolarization and the AP upstroke and is therefore activated at more negative E_m, to the atria in which I_{CaL} is predominantly involved in the AP plateau.

Although the peripheral or paranodal SAN region often has intermediate molecular and functional properties compared to the central SAN and atrial myocardium, recent work by Chandler *et al*. has revealed increased expression (at the mRNA level) of several K^+ channels and accessory subunits in the peripheral human SAN compared to both the central SAN and atria. These include greater expression of Kv4.2, Kir6.1, TASK1, SK2, and KCNE3 (formerly MiRP2) (101). The functional significance of these channels in the peripheral SAN remains unknown.

A key feature of the SAN is its ability to overcome the source-sink mismatch to activate the surrounding atrial myocardium. Differential expression of gap junction proteins plays an important role in this phenomenon. Gap junctions, comprised of connexins (Cx), are non-specific ion channels that electrically couple neighboring myocytes and allow an AP to propagate from cell to cell. The central SAN is devoid of both Cx40 and Cx43 (the large- and medium-conductance isoforms, respectively, responsible for cell-cell coupling in the working myocardium), and instead, the small conductance Cx45 is expressed (101, 225, 477). Therefore, the central SAN myocytes are relatively weakly coupled, which results in slow conduction through the node, but importantly, provides electrical insulation from the surrounding hyperpolarized atrial myocardium. Toward the periphery, electrical coupling improves with expression of both Cx43 and Cx45. Stronger coupling at the periphery of the SAN allows the SAN periphery to drive the atrial myocardium.

SAN Dysfunction

Sinus node dysfunction, also referred to as sick sinus syndrome (SSS) is a congenital or acquired pathology of the SAN. SAN dysfunction can manifest clinically as sinus

bradycardia, sinus pause, sinus arrest, and tachy-brady syndrome (SAN dysfunction in the setting of atrial fibrillation, AF). SAN dysfunction remains one of the most common indications for permanent pacemaker implantation (335).

Inherited Syndromes—As discussed below, SAN dysfunction is primarily a disease of aging (271). However, mutations affecting the voltage clock (*HCN4, SCN5A*), the Ca^{2+} clock (*RyR2, CASQ2*), or both (*ANK2*) have been identified and can be a primary cause of SAN dysfunction and will be highlighted here. For a more comprehensive discussion of genetic causes of SAN dysfunction and conduction system disease, see reviews by Park and Fishman (375) and Nof *et al*. (360).

HCN4: HCN4 is the major isoform responsible for I_f in the human SAN and mutations in HCN4 have been identified in patients with SAN dysfunction (330, 361, 437, 497). A single nucleotide deletion in HCN4 (1631delC) was identified in a patient with bradycardia and chrontropic incompetence (the inability to increase heart rate with increased activity) (437). Accordingly, the 1631delC mutant lacks the cyclic nucleotide binding domain, making it unresponsive to cAMP. Additional mutations have been identified in patients with bradycardia, including 2 missense mutations that result in HCN channels that activate at more hyperpolarized voltages and have smaller currents during diastolic depolarization (330, 361).

Nav Channels: Although the cardiac Na channel is expressed only in the periphery, but not the central SAN (101, 477), 14 SCN5A mutations have been linked to inherited forms of SAN dysfunction (414). SCN5A mutations associated with SAN dysfunction have been shown to result in non-functional channels, reduced I_{Na} current density, or altered biophysical properties of the channel which result in a narrowing of the I_{Na} current window (46, 456). Single cell simulations revealed that SCN5A mutants had little impact on the pacemaking in central SAN cells, but slowed pacemaking in the periphery. Interestingly, two-dimensional tissue simulations revealed that reduced I_{Na} in the periphery exposed the central SAN to more hyperpolarized E_m, thus slowing the pacemaker rate of the central SAN and predisposing to sinus node exit block, both clinical features of sinus node dysfunction (93).

Ca^{2+} Handling Proteins: As discussed above, the Ca^{2+} clock is an important contributor to diastolic depolarization and pacemaking in the SAN. Therefore, it is not surprising that mutations in Ca^{2+} handling proteins that give rise to catecholaminergic polymorphic ventricular tachycardia (CPVT, see also His-Purkinje System below) are also associated with sinus bradycardia. Mutations in RyR2 (the main SR Ca^{2+} release channel in cardiomyocytes) have been identified in patients with CPVT and SAN dysfunction (59, 391). CASQ2 encodes cardiac calsequestrin, the major Ca^{2+} binding protein within the SR. Mutations in CASQ2 are associated with aberrant SR Ca^{2+} release, CPVT, and sinus bradycardia (390). These genetic causes of SAN dysfunction lend further support to the Ca^{2+} clock hypothesis of SAN pacemaking.

ANK-B: ANK2 encodes ankyrin-B, an adaptor protein responsible for targeting ion channels and transporters to specialized membrane domains (333). Mutations in ANK2 are

associated with long QT syndrome (334) and SAN dysfunction (279). Heterozygous mice ($AnkB^{+/-}$) also have SAN dysfunction and reduced expression and/or abnormal targeting of NCX, Na^+/K^+ ATPase (NKA), IP3 receptors, and Cav1.3 (279). Accordingly, a reduction in I_{NCX} and I_{CaL} were also observed in isolated SAN cells from $AnkB^{+/-}$ mice. Therefore, mutations in ANK2 may lead to SAN dysfunction via both the voltage and Ca^{2+} clocks.

Acquired Syndromes

Aging: SAN dysfunction is largely a disease of aging, the incidence of which increases exponentially with age (271). Previous reports primarily attributed SAN dysfunction in the elderly to fibrosis and structural remodeling of the atria (132, 283). However, more recent studies have challenged this notion and have not confirmed the presence of SAN fibrosis in aged human, cat, or rat hearts (7, 581). On the other hand, specific evidence for age-related remodeling of ionic currents and ion channels in the SAN is mounting. For example, a decrease in AP upstroke velocity in the SAN periphery of aged hearts is believed to be a consequence of an age-related decrease in I_{Na} (8). Indeed, a decrease in expression of Nav1.5 has been demonstrated in the SAN of aged rat hearts (581). As discussed above in regard to SCN5A mutations, reductions in I_{Na} in the SAN periphery can lead to exposure of the central SAN to hyperpolarized E_m, thus slowing the central pacemaker rate (93).

An age-related decrease in Kv1.5 (I_{Kur}) in the rat SAN has also been found (478), which may partly explain the observed increase in AP duration with aging (8). In the guinea pig heart, an age-related reduction in I_{CaL} was observed, commencing in the central SAN and continuing on to the periphery (242). This reduction in I_{CaL} leads to reduced depolarization reserve and excitability of the SAN. A loss of Cx43 has also been documented in the aged guinea pig SAN (243), which may be partly responsible for SAN exit block, a feature commonly observed in age-related SAN dysfunction.

Interestingly, fibrosis and ion channel remodeling may not be mutually exclusive mechanisms. Mice heterozygous for *SCN5A* (responsible for Nav1.5 and I_{Na}) have age-related fibrosis in the SAN (210) as well as in atria and ventricles (507). Thus, it is reasonable to assume that structural and ionic remodeling may synergistically contribute to SAN dysfunction in the aged population.

Heart Failure: SAN dysfunction and severe bradycardia are responsible for a significant number of deaths in heart failure (HF) patients, especially patients with advanced HF (164, 464). Indeed, widespread remodeling of ion channels has been documented in several HF models. For example, downregulation of HCN2 and HCN4 has been found in the SAN of the failing canine heart (pacing-induced HF) (595). In a rabbit model of pressure and volume overload HF, a decrease in I_f and I_{Ks} in the SAN has been reported (517). Extensive ionic remodeling has also been observed in the SAN of the failing rat heart following myocardial infarction (580). Recently, Swaminathan et al. revealed a novel mechanism of SAN dysfunction in a mouse model of AngII-induced HF that implicates oxidized CaMKII (470). Briefly, they found that in HF activation of NADPH oxidase leads to an increase in oxidized CaMKII, which triggers apoptosis in SAN myocytes. Mathematical modeling revealed that SAN apoptosis leads to a decrease in SAN cell numbers, resulting in reduced depolarizing

source current and increased electrotonic loading of the surviving SAN myocytes. The authors also found elevated oxidized CaMKII in HF patients who required pacemaker implantation as well as in right atrial tissue from canines with pacing-induced HF (470). Thus, multiple mechanisms including ion channel remodeling, structural remodeling, and increased SAN apoptosis may contribute to SAN dysfunction in HF.

Atrium

Function

The first phase of the cardiac cycle, atrial contraction, is initiated by the P wave of the ECG, which represents electrical depolarization of the atria. Atrial depolarization then causes contraction of the atrial musculature. Contraction of the atria occurs late in ventricular diastole, when the drop in ventricular pressure and increase in atrial pressure allows opening of the atrioventricular valves and rapid emptying of the contents of the atria into the ventricles. Normally atrial contraction confers a minor, additive effect toward ventricular filling. However, atrial contribution in humans appears to be more significant during exercise, during fast heart rates, with aging, and particularly in patients with heart disease (14). Loss of normal electrical conduction in the heart, as seen during AF, may abolish atrial systole.

Ionic Mechanisms and Molecular Bases

During a normal heartbeat, spontaneous SAN depolarization activates the neighboring atrial myocardium. Atrial E_m depolarization is accomplished via activation of the voltage-dependent Na^+ channels, which carry I_{Na} that produces the rapid AP upstroke (phase 0) and favors rapid atrial conduction velocity (also permitted by Cx43, the major cardiac connexin found in the working myocardium of atria, and strong expression of Cx40). Subsequent activation of L-type Ca^{2+} channels produces a small influx of Ca^{2+} into the cell (I_{CaL}), which triggers a much larger Ca^{2+}-induced Ca^{2+} release from the SR through the cardiac RyRs, thus initiating contraction, as the released Ca^{2+} binds to the myofilaments. The Ca^{2+} transient also feeds back to cause I_{CaL} Ca^{2+}-dependent inactivation to prevent excessive Ca^{2+} loading. For atrial myocyte relaxation to occur, Ca^{2+} has to be extruded from the cell via the electrogenic NCX and plasmalemmal Ca^{2+}-ATPase, and re-sequestered into the SR via the SR Ca^{2+}-ATPase (SERCA). The latter is controlled by the inhibitory proteins PLB and sarcolipin. K^+ channels are mostly responsible for atrial E_m repolarization. The transient outward K^+ current (I_{to}) produces a rapid early repolarization (phase 1) immediately following the AP upstroke, while the delayed-rectifier K^+ currents with slow, rapid, and ultra-rapid activation kinetics (I_{Ks}, I_{Kr} and I_{Kur}, respectively) and the Na^+–K^+ ATPase current (I_{NKA}) control AP plateau (phase 2), repolarization (phase 3), and APD. The basal- and muscarinic-receptor-activated inward-rectifier K^+ channels responsible for I_{K1} and $I_{K,ACh}$, respectively, predominantly conduct at negative E_m and as such are critical for maintaining a normal resting E_m (RMP, phase 4). Notably, I_{Kur} and $I_{K,ACh}$ contribute little to ventricular repolarization, providing opportunities for atrial-selective antiarrhythmic drugs, as discussed below. Atrioventricular differences in I_{Na} inactivation properties also confer atrial selectivity to certain Na channel blockers, including ranolazine (88). Figure 3 depicts simulated atrial APs and CaT (from (193)) and the major ionic currents that are

active during the cardiac cycle. The genes encoding the ion channel subunits that compose these currents are also summarized in Figure 3.

Atrial Regional Heterogeneity

Atrial APs exhibit regional variability. Within the canine right atrium, myocytes from different regions show systematic variations in AP morphology and duration that reflect spatial variation in ionic current densities, with voltage- and time-dependent properties being constant across regions (169). Namely, cells from the crista terminalis have a "spike-and-dome" morphology and the longest APD (corresponding to the largest I_{CaL}). Atrial appendage and pectinate muscle cells have intermediate APDs, with appendage cells having a small phase 1 and high plateau (due to a small I_{to}); and cells from the atrioventricular ring area have the shortest APD (corresponding to the smallest I_{CaL}). I_{K1} and I_{Kur} are similar in all regions, whereas I_{Kr} is larger in atrioventricular ring cells compared with other regions. Three different outward current patterns (types 1–3) were observed in human atrial appendage myocytes, based on the relative magnitude of transient outward and delayed rectifier K^+ currents (Figure 4). Type 1 was the most abundant, and characterized by a large I_{to} and a clear I_K, type 2 was the least abundant and displayed only I_K, whereas a prominent I_{to} and negligible I_K characterized type 3. Consistent differences in AP morphology were observed, with type 2 cells having a higher plateau and steeper phase 3 slope and type 3 cells showing a triangular AP and lesser phase 3 slope compared with type 1 cells (541).

The left atrium has shorter APs and refractory period compared to the right atrium, which has been attributed to larger I_{Kr} (284). I_{Ks}, I_{Kur}, I_{to}, and I_{CaL} were all comparable in the canine right and left atria (284), although I_{Kur} was found to be ~20% larger in myocytes from the right *vs.* left atrium of sinus rhythm patients (94). The AP was even shorter in the pulmonary vein (PV) myocytes. I_{Ks} and I_{Kr} were greater in the PV, consistent with greater Kv11.1 (ERG) and Kv7.1 (formerly KvLQT1) abundance, whereas transient outward K^+ current and L-type Ca^{2+} current were significantly smaller. Inward rectifier current density in the PV myocytes was approximately half that in the left atrium (and Kir2.3 was less expressed), potentially accounting for the less negative RMP in PVs (157, 327). Regional differences in atrial repolarization may be important in AF, as discussed below.

Atrial Fibrillation: Mechanisms and Ionic Remodeling

AF is the erratic and rapid activation of the atria, which is reflected in the ECG by an undulating baseline that replaces the regular P waves, and irregular QRS complexes. AF is the most common sustained arrhythmia encountered in clinical practice, with a prevalence of 1–2% in the general population, which increases with age. The disease is associated with increased morbidity and mortality and is responsible for over one-third of all embolic strokes. Current drugs for AF treatment have limited efficacy and may increase the risk of malignant ventricular arrhythmias. Thus it is likely for the disease to progress from paroxysmal AF (pAF) to extensive electrical, structural, contractile, and neurohormonal (mal)adaptive responses leading to chronic AF (cAF).

Animal and clinical studies have suggested that AF is a reentrant arrhythmia sustained by reentrant circuits propagating in a remodeled atrial tissue substrate (238). Rapid electrical

impulse generation outside of the SAN (ectopic/triggered activity), particularly around the pulmonary veins, can trigger reentry in a vulnerable substrate or, when occurring repetitively at high frequency, contribute to AF maintenance by serving as a driver through so-called 'fibrillatory conduction'. These mechanisms are thoroughly reviewed in a recent article by Wakili *et al*. (531).

Ectopic activity from atrial foci could result from automatic firing, which occurs when an increase in time-dependent depolarizing inward currents carried by Na^+ or Ca^{2+} or a decrease in repolarizing outward K^+-currents causes progressive time-dependent cell depolarization. When threshold potential is reached, the cell fires, producing automatic activity (Figure 5). Triggered activity also results from early or delayed afterdepolarizations (EADs or DADs) occurring during or after repolarization of the atrial AP. EADs during AP phase 2 occur predominantly at slow heart rates in the setting of reduced repolarization reserve and prolonged APD due to increased inward Ca^{2+} and Na^+ or decreased outward K^+ currents. Although several pathological conditions resulting in reduced repolarization reserve (e.g., long-QT syndrome) have been associated with increased susceptibility to AF induction, the role of phase-2 EADs during fast atrial rates in AF is uncertain. On the other hand, EADs can also arise from Ca^{2+}-handling abnormalities that activate depolarizing NCX current (late phase-3 EADs), which have been implicated in the initiation of AF (87, 376) via non-equilibrium reactivation of I_{Na} (156). DADs arise from a transient inward current I_{ti} through forward mode NCX, which is evoked by diastolic increase in $[Ca^{2+}]_i$ due to abnormal spontaneous Ca^{2+} release from the SR (Figure 5).

Reentry can occur when an electrical impulse is able to re-excite areas that have already recovered, thereby providing a perpetuation of electrical activity. Reentry can be caused by a fixed anatomical obstacle, or be functional reentry. For reentry to be sustained, all points in the reentrant path need to become excitable before the arrival of the reentrant impulse (termed ‘excitable gap’). When wavelength (i.e., the distance an impulse travels within a single refractory period) decreases due to shortening of the effective refractory period (ERP) or due to conduction slowing (Figure 5), reentry will be more likely and more reentrant circuits can fit in the same area, making AF more stable and less likely to terminate.

Changes in atrial function or structure (collectively termed ‘atrial remodeling’) can support AF induction and/or maintenance. Several studies have investigated the molecular and ionic mechanisms involved in the remodeling of the atria of patients with AF, and suggest that structural, electrophysiological, and contractile remodeling are critical factors in the disease progression, i.e., they contribute to the development of a substrate that facilitates the tendency for persistence of AF (AF begets AF) (348, 531). Structural remodeling involves changes in atrial myocyte and tissue morphology (e.g., cell hypertrophy, fibrosis) (148, 348, 558). Electrical remodeling includes changes in Ca^{2+}- and K^+-currents leading to shortening of the APD and effective refractory period (ERP), and loss of rate adaptation of both atrial repolarization and refractoriness (558). Typically, the human atrial APD at 90% repolarization (APD_{90}) shortens when paced at faster frequencies, but in myocytes isolated from cAF patients this shortening is severely attenuated. A growing body of experimental evidence points to perturbations in intracellular Ca^{2+} handling as important players in AF-induced atrial remodeling (147, 149), with intracellular Ca^{2+} transients (CaTs) being

reduced, despite unaltered SR Ca^{2+} content (193, 295, 350, 521). CaTs decay more slowly in cAF compared to sinus rhythm (193, 521). Elevated diastolic $[Ca^{2+}]_i$ has been reported and attributed to enhanced leak of Ca^{2+} from the SR (350). CaT amplitude increases with the pacing rate in normal atrial myocytes (314), but we importantly showed that this is impaired when simulating cAF conditions (193). Our simulations also indicated that APD rate adaptation in sinus rhythm atrial cells involves accumulation of intracellular Na^+ ($[Na^+]_i$) at high frequencies, which causes outward shifts in NCX and NKA currents. The model also predicted that E-C coupling remodeling in cAF would reduce Na^+ accumulation, thus causing a blunted APD rate-dependent response (193). Myofilament protein changes in AF are also likely to contribute to atrial contractile dysfunction (40).

Here we summarize the current knowledge of the ionic bases underlying AF-associated electrical and Ca^{2+} handling remodeling, especially focusing on data from cAF patients (Table 1, reviewed previously in (196)). Figure 3 provides a graphical representation of the main changes occurring in the electrophysiological and Ca^{2+} handling processes in human cAF. Understanding the molecular mechanisms of excitation-contraction-coupling remodeling in the fibrillating human atria is important to identify new potential targets for AF therapy.

EC coupling remodeling can occur at the level of ion channels/transporters expression, or by modification of ion channel/transporter properties (for example, trafficking or phosphorylation). Altered protein kinase and phosphatase activity may importantly contribute to EC coupling remodeling in AF. Indeed, CaMKII has been found to be more expressed and more phosphorylated in human cAF (350, 481). Similar PKA activity was found in cAF *vs.* sinus rhythm in goats (199), but El-Armouche *et al.* detected a higher total activity of type 1 and type 2A phosphatases in human cAF, causing inhomogeneous changes in protein phosphorylation in different cellular compartments (160). This may specifically amplify PKA and CaMKII effects on certain targets without having significant effects on others (e.g., higher phosphatase activity/lower phosphorylation in thick *vs.* thin myofilaments, cell membrane *vs.* SR) (160). Thus, there is growing interest in the potential role of CaMKII and protein phosphatase inhibitors in preventing arrhythmogenic remodeling in cAF.

Nav Channels—Bosch *et al.* reported that I_{Na} density and voltage-dependence of activation were not altered in human AF (69), the steady-state inactivation was shifted to the right (69), and no changes were detected in mRNA levels of the Na^+ channel gene *SCN5A* (82). In contrast, Sossalla *et al.* provided recent evidence that expression of Nav1.5 and peak I_{Na} density is decreased (slightly) in the atrial myocardium of patients with cAF (459). Although it is unclear whether altered fast I_{Na} contributes to the electrical remodeling in human AF, Na^+ channel blockers with E_m- and frequency-dependent action preferentially suppress AF because of the high excitation rate and less negative atrial *vs.* ventricular RMP, which promote drug binding in atria. Vernakalant and ranolazine, which mainly block atrial Na^+ channels, are clinically effective (402). The former is in clinical use for cardioversion of AF in Europe, the latter has efficacy for AF and is being tested in prospective clinical trials.

It has recently been shown the late Na^+ current component (I_{NaL}) is significantly increased in cAF patients (459). Sossalla *et al.* (459) proposed that this increase could be due to the increase in neuronal Na^+ channel isoforms (Nav1.1 expression is increased), or mediated by CaMKII, which is increased in AF (350, 481) and known to regulate I_{NaL} (527), or caused by oxidative stress (329, 529). However, our simulations suggested that an increased I_{NaL} does not contribute significantly to repolarization in cAF, where the overall APD_{90} was still shorter than that in normal healthy cells (193). On the other hand, an increase in I_{NaL} may cause cellular Na^+ and Ca^{2+} overload and lead to contractile dysfunction and electrical instability (via reverse-mode NCX) (49).

Cav Channels—Reduction in I_{CaL} density (−50% *vs.* sinus rhythm) is one of the most consistent features of electrophysiological remodeling in human AF (as seen in (112, 148, 193, 509, 521, 560)). Christ *et al.* (112) demonstrated that decreased I_{CaL} density in cAF is not accompanied by altered expression of the corresponding α1c and β2a channel subunits (although other studies found different results (83)), and proposed that lower basal I_{CaL} is due to decreased channel phosphorylation in AF, which results from an altered ratio of protein kinase/phosphatase activity in favor of increased phosphatase activity. An analogous explanation was proposed for the blunted effect of CaMKII inhibition on I_{CaL} in human cAF (350). It has been shown that blocking I_{CaL} with nifedipine in normal human atrial cells results in an AP characteristic typically seen in AF (509) with respect to morphology, duration and impaired rate-dependent adaptation, i.e., reduction in I_{CaL} seems to be a critical component of the remodeled atrial electrical phenotype. However, Workman *et al.* found that nifedipine did not significantly alter ERP in sinus rhythm myocytes (although APD was shorter), thus supporting the idea that I_{CaL} downregulation may not be sufficient by itself to explain the remodeled atrial electrical phenotype (560). There is no evidence of I_{CaT} in human atrial myocytes (289, 455), but I_{CaT} is present in atrial myocytes of other species (290, 351, 430).

HCN Channels—The hyperpolarization-activated pacemaker current, I_f, has been found to be increased in human AF compared to sinus rhythm, at least at the mRNA level (274), and could contribute to ectopic atrial pacemaker activity. However, functional evidence for I_f involvement is lacking at present.

Kv Channels—Human cAF is associated with strong reduction of I_{to} density (69, 79, 94, 148, 191, 510, 560) and downregulation of its channel α-subunit Kv4.3 (82, 84). I_{Kur} was reduced in cAF (79, 94, 113, 148, 510), paralleled by diminished expression of Kv1.5 (82, 84, 510). However, others have reported no changes in I_{Kur} density (69, 191, 560). Inconsistent results regarding I_{Kur} function have been commented on previously by Christ *et al.* and attributed to different strategies for identification of I_{Kur} (e.g., pharmacological or with I_{to}-inactivating prepulse), and to a fraction of I_{Kur} that is not accounted for by Kv1.5 (113). The reduction in I_{to} and I_{Kur} explains the slight prolongation in earlier phases of the AP (193, 508).

It has been shown that CaMKII (increased in cAF) positively regulates I_{to} in human atrial myocytes in acute conditions, as the application of the CaMKII inhibitor KN-93 caused loss of channel function (481). The authors speculated that, by reducing the extent of inactivation

of I_{to}, upregulation of CaMKII during AF reduces Ca^{2+} influx and therefore minimizes Ca^{2+} overload. On the other hand, CaMKII overexpression in cAF may impact channel expression, thus contributing to I_{to} downregulation, as recently shown in CaMKII-overexpressing transgenic mice (528).

Experimental evidence suggests that block of I_{Kur} enhances force of contraction of isolated human atrial trabeculae both in patients in sinus rhythm and AF (428, 449, 552). We have recently predicted that block of I_{Kur} results in prolongation and elevation of the AP plateau, which augments the CaT amplitude that would elicit a positive inotropic effect (193). Taken together, these studies suggest that I_{Kur} might be a potentially useful atrial-specific target to potentially counteract hypocontractility associated with cAF. A slight AP prolongation associated to I_{Kur} blockade may also be beneficial. Numerous compounds have been screened for high Kv1.5 selectivity, characterized electrophysiologically in isolated cardiac myocytes and tissue, and tested for their antiarrhythmic activity in various animal models of AF. Despite these efforts, proof-of-concept of antiarrhythmic efficacy in human is still lacking (402).

The delayed rectifier K^+ currents have proven much harder to record and study in isolated human atrial cells (171). Nevertheless, their contribution is likely to be small in cells that lack an appreciable plateau phase (541). The block of the rapidly activating delayed rectifier K^+ current, I_{Kr}, has been shown to prolong human atrial APD in the late phase of repolarization by a small amount (552), and to date no experimental evidence has suggested its involvement in AF-induced electrical remodeling. Recently, Caballero *et al.* provided the first demonstration that cAF significantly increased the amplitude of the slow delayed rectifier K^+ current, I_{Ks}, in both atria (94). They suggested that I_{Ks} increase could contribute to cAF-induced shortening of APD and to further promote fibrillatory conduction, especially with current accumulation at high frequencies.

Inward Rectifying Channels—In cAF, increases in both current density (146, 148, 510, 523, 560) and mRNA levels (146, 148) have been reported. Increased I_{K1} causes a more negative resting E_m in cAF *vs.* sinus rhythm human atrial myocytes (146, 193, 523).

Patients with chronic AF exhibit agonist-independent constitutive $I_{K,ACh}$ activity that contributes to the enhanced basal inward rectifier current and may result from abnormal channel phosphorylation by PKC (145, 146, 523). Constitutively active $I_{K,ACh}$ is considered to support the maintenance of AF, together with increased I_{K1}, by stabilizing reentrant activity sustained by rotors (faster activation, less meander) (374). The recently reported $I_{K,ACh}$ blocker NTC-801 was suggested to exert antifibrillatory action by atrial-selective ERP prolongation (310), but no data are yet available in native human tissue (402).

The ATP-sensitive K^+ (I_{KATP}) channels generate an inward rectifying current that activates with a decrease in intracellular ATP concentration (589). Gene expression and electrophysiological studies in patients with AF demonstrated reduced mRNA levels of Kir6.2 (84) and current activation (28), but increased current was also reported (561). It is conceivable that structural heart disease and atrial dilation could alter the metabolic and mechanosensitive gating of KATP channels, thus providing a substrate for AF (371).

Recent studies show predominant atrial expression of mRNA in humans for several other K^+ channels (TWIK1 and TASK1) that function similarly to the voltage-independent inward rectifying K^+ channels responsible for I_{K1} (178, 296, 425). TWIK1 and TASK1 belong to a family of two-pore domain K^+ channel proteins (K_{2P}) that are responsible for background K^+ currents and can be regulated by pH, oxygen, stretch, temperature, drugs, lipids, and second messengers (205, 296, 425). Inhibition of K_{2P} channels in human atria is expected to prolong atrial APD and increase the effective refractory period, which suggests the possibility of targeting these channels in atrial-selective anti-arrhythmogenic drugs.

Ca^{2+}-activated K^+ Channels—Although there is controversy regarding the role of small conductance Ca^{2+}-activated K^+ (SK) channels in atrial repolarization under physiological conditions (reviewed by (311)), I_{SK} does appear to contribute to AF-related remodeling. An increase in I_{SK} due to increased SK2 trafficking has been reported in a rabbit atrial model mimicking PV ectopy (373). SK2 expression was found increased in the PVs in a canine atrial tachypacing model, in which I_{SK} increase resulted from increased SK1 expression (398). Overexpression of SK3 in mice also promotes AF (313). Upregulation of I_{SK} is expected to result in abbreviated APD and ERP, thus promoting reentry. On the other hand, *KCNN2* null mice have AF resulting from prolonged APD and triggered activity (292).

Ca^{2+} Handling Proteins—Increased expression (160, 429, 521) and abnormal function of NCX (193, 521) are implicated in human AF pathophysiology. An increase in I_{NCX} may be an adaptive response to cellular Ca^{2+} loading and contribute to diminish the Ca^{2+} overload induced by rapid atrial activation (along with I_{CaL} downregulation). Indeed, the decay rate of caffeine-evoked CaT (attributable to Ca^{2+} removal by NCX) is shown to be faster in human cAF *vs.* sinus rhythm myocytes (193, 350, 521). Na^+ overload-induced Ca^{2+} influx via reverse-mode NCX has been implicated in Ca^{2+} overload and related arrhythmogenesis, whereas increase Ca^{2+} extrusion via forward-mode has been linked to DADs (49, 393). Indeed, Na^+ and Ca^{2+} loading are more favored at increased atrial rates (i.e., during AF). However, more studies are needed to assess whether DADs are important in initiating arrhythmias in AF, and the underlying role of NCX in mediating them, since an increased I_{K1} in cAF will tend to oppose the occurrence of such DADs. These studies will help determine if blocking NCX represents a novel therapeutic strategy in suppressing arrhythmia triggers in cAF.

Spontaneous Ca^{2+}-release events (Ca^{2+} sparks) and Ca^{2+} waves through leaky RyR channels have been reported in myocytes from cAF patients (103, 350, 518, 521) despite unaltered SR Ca^{2+} content. One potential contributor to RyR hyperactivity may be oxidative stress, which is known to play a critical role in AF pathophysiology (329) and increase RyR open probability. Neef *et al.* suggested that the CaMKII-dependent increase in SR Ca^{2+} leak caused by RyR hyperphosphorylation in AF is a potential arrhythmogenic mechanism (350), because elimination of Ca^{2+} via inward I_{NCX} could lead to cell depolarization and cause DADs. Voigt *et al.* measured directly single RyRs isolated from cAF patients and demonstrated a higher channel open probability in cAF that responded to CaMKII inhibition (522). Thus CaMKII inhibition may reduce the propensity for atrial arrhythmias.

A decrease in SERCA activity, associated with lower SERCA protein expression (160, 521), is evident in human cAF and explains the slower CaT decay compared to sinus rhythm (160, 193, 521). On the other hand, reduced inhibition of SERCA by hyperphosphorylated PLB (160) in cAF could help to maintain a normal SR Ca^{2+} load despite increased RyR activity.

NKA—Workman *et al*. found no difference in NKA pump current in myocytes from cAF patients compared to sinus rhythm, and concluded that I_{NKA} is not involved in AF-induced electrophysiological remodeling in patients (559). Our simulations show lower NKA current underlying the AP because of reduced Na^+ loading in cAF. Intracellular $[Na^+]$ changes may contribute to the human cAF phenotype, as we postulated in our modeling study (193) but have not yet been measured.

Ankyrin-B—Ankyrin-B (encoded by *ANK2*) is an adaptor protein expressed in excitable cells that targets ion channels (e.g., Na^+ and Ca^{2+} channels), transporters (e.g., NKA and NCX), and signaling molecules to specific membrane domains. Ankyrin-B loss-of-function mutations in humans lead to Long QT syndrome, AF, sinus node dysfunction and stress-induced ventricular arrhythmias (334). Recently, reduced ankyrin-B expression has been demonstrated in atrial samples of patients with paroxysmal AF, and supported an association between ankyrin-B and AF (125). A new potential molecular mechanism underlying ankyrin-associated AF has been proposed involving disrupted Cav1.3 (atrial L-type Ca^{2+} channels) membrane targeting in atrial myocytes (125).

Connexins—While an important role for connexins in AF is strongly supported by connexin gene mutations associated with AF (see below), controversial results on the role of connexin in clinical and experimental AF models have been reported (reviewed in (256)). Alterations in both total connexin expression and distribution have been described, but the results show wide variations, with opposing results even within the same model. Transgenic animal models have also reported contradictory results, with studies indicating a clear increase (207) or no change (494) in atrial tachyarrhythmia susceptibility with Cx40 knockout. Small-molecule drugs enhancing gap junction conductance have been developed as potential treatments for AF, and lead to improvement in some models (ischemia and mitral valve disease–related AF). However, little or no change is reported in other clinically relevant models (200, 278, 451). Thus, the role of connexin abnormalities in AF and the potential value of modulating connexin function to treat AF remain unclear.

While gap junctional coupling is usually considered to be the primary mechanism for AP propagation, there is evidence that other mechanisms are important. In particular, absence or reduction in Cx43 function produced only a moderate reduction of cardiac propagation velocity in mice (201, 582). One possible explanation for these experimental findings is that ephaptic (i.e., field effect) coupling may be significant. Field or ephaptic coupling refers to the initiation of an AP in a non-activated downstream cell by the electrical field caused by an activated upstream cell. Computer simulations showed that, under certain conditions, local accumulation of ions in the junctional extracellular cleft may alter local membrane potential, thus indicating that ephaptic coupling may play a role, but strongly depends on parameters like Na^+ channel conductance and distribution, and the width of the extracellular cleft at the intercalated disk (297, 336). Membrane-tunneling nanotubes serving as cytosolic

bridges between cells (211) were recently suggested as another mechanism of electrical cell-to-cell coupling. This theory, however, still needs further investigation.

Regional Heterogeneity in Atrial Remodeling—Caballero *et al.* have recently looked at differences in current density and AF-induced alterations in the right *vs.* left human atrium. They found heterogeneity in the repolarizing currents between the atria in sinus rhythm, and demonstrated that cAF reduced the I_{to} amplitude and density more markedly in the left than in the right atrium, thus creating a right-to-left gradient, whereas I_{Kur} was more markedly reduced in the right than in the left atrium, thus dissipating the left-to-right gradient detected in sinus rhythm (94). They also provided the first demonstration that cAF significantly increased the amplitude of the slow delayed rectifier K^+ current, I_{Ks}, in both atria (94). They suggested that I_{Ks} increase could contribute to cAF-induced shortening of APD and to further promote fibrillatory conduction, especially with current accumulation at high frequencies. However, the data concerning intra-atrial heterogeneities in repolarizing currents in human atrial myocytes are still limited, and it is unclear whether and how these changes may contribute to the perpetuation of arrhythmia (193). Recently, Voigt *et al.* found significant left-to-right gradients in I_{K1} and constitutively active $I_{K,ACh}$ in patients with paroxysmal AF, which were dissipated in cAF, raising the idea that this may contribute to left-to-right dominant frequency gradients that are often more evident in paroxysmal AF *vs.* cAF (523). It has also been shown that cAF increases the effects of β1-adrenoceptor stimulation on repolarizing currents by means of a chamber-specific upregulation of the receptors, which are overexpressed in the left *vs.* right atria. This, together with the ion channel derangements produced by cAF, could shorten the APD thus contributing to the long-term stabilization of the arrhythmia (188).

Role of the Autonomic Nervous System in AF

The autonomic nerves extensively innervate the heart, and the nervous system is important for cardiac function and arrhythmogenesis by modulating many ion channels. Indeed, simultaneous sympathovagal discharges commonly precede arrhythmias, and both sympathetic and vagal activation have been shown capable of producing proarrhythmic atrial and ventricular electrophysiological changes (55, 142) – see also ventricular section entitled “Role of the Autonomic Nervous System in Ventricular Arrhythmia”. Both the stellate ganglion (a major source of cardiac sympathetic innervation) and the vagal nerves have complex structures containing mixed nerve types (reviewed in (106)). In addition to the complex anatomic and physiological interactions between various nerve structures, cardiac autonomic innervation is also the subject of remodeling, especially during disease states, as witnessed by the increased sympathetic nerve densities found in patients with cAF (353). Indeed, abnormal autonomic innervation may be important in the initiation and maintenance of AF, and modulating autonomic function to reduce autonomic innervation or outflow has shown useful for AF control (see review (106)). Intrinsic cardiac nerves are found mostly in the atria and are intimately involved in atrial arrhythmogenesis. Histological study of human pulmonary vein–left atrium junction showed that numerous autonomic nerves are present (475, 503). Adrenergic and cholinergic nerves are strongly colocalized at tissue and cellular levels, which makes it difficult to selectively eliminate one or the other arms of the autonomic nervous systems, e.g., via catheter ablation (475).

AF associated with ion channel genetic mutations

The familial form of AF is uncommon. However, in the past decade mutations in various ion channels have been identified and linked the genetic form of AF with ion channelopathies (see recent reviews (95, 312)). Mutations in a number of genes have been associated with AF, but they are rare and do not explain the majority of cases of familial AF. These include genes encoding K^+ (*KCNQ1*, *KCNA5*, *KCNE5*, *KCNJ2*, and *KCNE2*) and Na^+ (*SCN5A*, *SCN1B*, *SCN2B*, and *SCN3B*) channels, K^+–adenosine triphosphate channels (*ABCC9*), nucleoporin-155 (*NUP155*), gap junction protein connexin 40 (*GJA5*), and atrial natriuretic peptide (*NPPA*).

Nav Channels—Both loss- and gain-of-function variants in *SCN5A* have been associated with AF (131), and loss-of-function mutations in Na channel β1 and β2-subunits (*SCN3B* and *SCN4B*) are associated with AF (368, 546). The electrophysiological mechanisms by which Na mutations cause AF are not clearly understood (312). Increased I_{Na} and I_{NaL} can induce triggered activity and stabilize high-frequency rotors. Conversely, reduced I_{Na} and I_{NaL} density can promote reentry by shortening APD and shortening the atrial reentry wavelength, but also destabilizes high-frequency rotors (264).

Kv Channels—A missense mutation in Kv7.1 (*KCNQ1*) resulting in the amino acid change S140G was first identified in a 4-generation family causing a gain-of-function phenotype that increases I_{Ks} when the mutated channel was expressed with the β-subunits KCNE1 (formerly minK) and KCNE2 (formerly MiRP1) (109). A *de novo* gain-of-function mutation (V141M) was found responsible for a severe form of AF and short-QT syndrome *in utero* (224). Interestingly, a missense *KCNQ1* mutation, R14C, was identified in one family with a high prevalence of hypertension (372). This caused a gain-of-function only when cells were placed in a hypotonic solution, suggesting that an environmental factor like hypertension, which promotes atrial stretch and thereby unmasks an inherited defect in ion channel kinetics, is required for AF to be manifested. Gain-of-function in I_{Ks} secondary to a mutation in *KCNE5* (encoding the KCNE5 or MiRP4 β-subunit) was also reported and associated with AF (403).

Mutations in *KCNE2* have been also identified and liked to familial AF. The mutation R27C caused a gain-of-function when coexpressed with Kv7.1, but had no effect when expressed with Kv11.1 (hERG), unlike long QT syndrome-associated *KCNE2* mutations (577). Mutations M23L and I57T were identified in patients with early-onset lone AF, and caused a significant gain-of-function effect upon coexpression with Kv7.1 and Kv7.1+KCNE1 (356). The mutation V17M in *KCNE3* was found in a proband with early-onset lone AF and led to gain-of-function of several cardiac currents (Kv4.3/KCNE3 and Kv11.1/KCNE3) (307). A gain-of-function mutation in Kir2.1, caused by a mutation in *KCNJ2*, was found in a family with AF (563). Overall, K^+ channel gain-of-function mutations are likely to initiate and maintain AF by reducing APD and ERP in atrial myocytes.

A KATP channel mutation has been shown to confer risk for adrenergic AF originating from the vein of Marshall (370), and it has been proposed that KATP channel deficit could play a broader role in the pathogenesis of electrical instability (371).

Loss-of-function mutations in *KCNA5*, the gene encoding Kv1.5, have been also linked to AF (114, 369, 575). In the first report, this loss of channel function was shown to translate into AP prolongation and EADs in human atrial myocytes, increasing vulnerability to stress-provoked triggered activity (369). Gain-of-function mutations in *KCNA5* have been found in patients with early-onset lone AF. This supports the notion that both increased and decreased K^+-currents enhance AF susceptibility (114).

Connexins—*GJA5* encodes connexin-40, a gap junction protein in the atrium that plays a critical role in mediating coordinated AP conduction via cell-to-cell electrical coupling. Mutations in this gene have been associated with AF (187, 557) (467), and their functional analysis revealed abnormal intracellular transport in addition to a reduction in electrical coupling between cells (187, 467). This can result in conduction heterogeneity, micro-re-entrant circuits, and AF.

Non-ion channels—A frame shift mutation has been identified in a large family with AF in the atrial natriuretic peptide precursor (*NPPA*). *NPPA* encodes atrial natriuretic peptide, which modulates ionic currents in cardiac myocytes and can play a role in shortening of the atrial conduction time, which could be a potential substrate for atrial re-entrant arrhythmias (222).

A mutation in *NUP155*, which encodes a member of the nucleoporins, has been associated with AF, characterized by a neonatal onset, with autosomal recessive inheritance (592). The mechanism by which *NUP155* may be associated with AF could be related to the modulation of Ca^{2+} handling proteins and ion channels and expression of its possible target genes, like HSP70.

AF associated with other monogenic diseases—AF has been described in other cardiac monogenic diseases as a concomitant disease, e.g., hypertrophic cardiomyopathy, in which the disease is probably related to structural changes in the atria caused by the underlying cardiac pathology. AF can also be present in other life-threatening ion channelopathies like long-QT syndrome (LQTS) (43, 307), Brugada syndrome (BrS) (338), and short-QT syndrome (SQTS) (134). A recent study demonstrated pleiotropy in *KCNQ1*, whereby a discrete missense mutation (R231C) is capable of both long-QT syndrome and familial AF (34). Additionally, a mutation at the same residue (R231H) was linked to familial AF in multiple unrelated families suggesting that mutations that disrupt voltage sensor of Kv7.1 and increase constitutive activity lead to higher AF susceptibility (33).

Atrioventricular Node

Function

The AVN is located at the base of the atrial septum, at the apex of an area known as the triangle of Koch (Figure 1A) (291). The triangle is bounded by the ostium of the coronary sinus, the tendon of Todaro and the tricuspid valve (Figure 6A). Two pathways lead into the compact AVN: the transitional zone and the inferior nodal extension, comprising the fast and slow pathways for AV conduction, respectively (460). This ‘dual pathway electrophysiology’ (332) refers to the fastest (and therefore ‘normal’) route of AP

propagation from the SAN through the AVN that uses the atrial septum and transitional zone, as opposed to the slowest pathway that uses the terminal crest and inferior nodal extension (232). Distal to the compact AVN is the penetrating bundle, which is embedded in the central fibrous body and emerges on the crest of the ventricular septum, where it becomes the His bundle.

The AVN serves several important functions, including providing a conduction delay between the atria and ventricles in order to allow atrial systole to take place before initiation of ventricular systole. The AVN also has a relatively long refractory period in order to protect the ventricles from atrial tachyarrhythmias by producing conduction block of high frequency atrial APs. Finally, the AVN can also serve as a back-up pacemaker if the SAN fails due to the intrinsic pacemaking ability of the AVN. Distinct ion channel and gap junction expression profiles throughout the nodal structures allow for the AVN to perform these diverse and vital functions.

Ionic Mechanisms and Molecular Bases

The compact AVN and inferior nodal extension are comprised of nodal-like (N) myocytes that have AP properties and ion channel expression somewhat similar to that of the central SAN (60, 197, 198, 342). APs from these myocytes have a relatively depolarized diastolic E_m (−50 to −60 mV), diastolic depolarization, a slow I_{CaL}-mediated upstroke, and relatively long APD (60, 342). Not surprisingly then, the N myocytes of the human compact AVN have similar ion channel expression to that of the human central SAN, including robust expression of HCN4 (I_f), decreased expression of Kir2.1 (I_{K1}), decreased expression of Nav1.5 (I_{Na}), and a phenotypic switch from Cav1.2 to Cav1.3 (I_{CaL}) compared to the working atrial myocardium (101, 178, 197). A few differences in ion channel expression (at the mRNA level) were observed, however, between myocytes of the compact AVN and central SAN in the human. Whereas the central SAN shows significantly decreased expression of Kv4.3 (I_{to}), Kv1.5 (I_{Kur}), and Kv11.1 (I_{Kr}) relative to the atrial myocardium (101), the compact AVN does not show such robust down-regulation of these K^+ channels and instead, shows a significant increase in expression of Kv1.4 and Kv4.2 (both I_{to}) compared to the atrial myocardium (197). This altered K^+ channel expression may suggest different ionic mechanisms responsible for early and late repolarization in the central SAN *vs.* the compact AVN. Differences in expression of key Ca^{2+} handling proteins between the human central SAN and compact AVN were also observed, with the SAN showing robust down-regulation of SERCA2 and RyR2 compared to the atrial myocardium (101), whereas the AVN has similar expression of SERCA2 compared to the atrium and only a slight downregulation of RyR2 (197). The functional significance of this differential Ca^{2+} handling protein expression remains unknown, but is interesting to consider from the standpoint of Ca^{2+} clock functionality in the SAN and AVN.

Although the AVN is not a primary pacemaker, if the SAN fails AVN pacemaking can occur, although at a slower rate. For example, Dobrzynski and colleagues observed a near doubling of the cycle length in the excised rabbit heart as pacemaking shifted to the AVN following SAN removal (152). It is thought that under normal circumstances, the hyperpolarizing electrotonic influences of the atrial myocardium prevent spontaneous AVN

activation and pacemaking. This conclusion results from studies in which the AVN was dissected from surrounding atrial and His tissue, resulting in a dramatic acceleration of rate (260). In the human, rabbit, and rat, HCN4 is abundantly expressed throughout the AVN (27) and is likely responsible for I_f in the AVN and thus an important player in pacemaking. Interestingly, knock-out of HCN4 not only causes sinus bradycardia, but also high-degree AV block (36), suggesting that I_f also plays an important role in normal AVN conduction.

AVN Heterogeneity: Ion Channel and Gap Junction Distribution

In addition to the compact node, the AVN is comprised of the transitional zone and inferior nodal extension (the fast and slow pathways into the compact node, respectively) and the penetrating bundle distal to the compact node (Figure 6A). The transitional zone is made up of atrio-nodal (AN) myocytes, the penetrating bundle is comprised of nodal-His (NH) myocytes, and the inferior nodal extension and compact node are mainly comprised of nodal-like (N) myocytes (198). As discussed above, N cells have nodal-like AP morphology and ion channel expression, whereas the AN and NH myocytes are more intermediate in nature. APs from AN and NH myocytes have more negative diastolic E_m compared to N myocytes and a faster AP upstroke (Figure 6B-5D) (60).

Although HCN4 is expressed throughout the AVN, Munk *et al*. showed that only approximately 10% of rod-shaped AN myocytes exhibit I_f, whereas nearly 100% of oval-shaped N and NH myocytes exhibit the current (342). Munk *et al*. also reported that 100% of AN myocytes exhibit I_{Na}, whereas only 30% of N and NH myocytes have I_{Na} (342). Accordingly, Nav1.5 is absent or poorly expressed in the inferior nodal extension and compact node (N myocytes), and has intermediate expression in the human transitional zone (AN myocytes) compared to the working atrial myocardium (197, 198, 583).

In addition to differential ion channel expression throughout the AVN, there is also a diversity of gap junction expression, which contributes to the emergent function of the AVN. It has been known since the early work of Pollack (389) that cell-cell coupling in the AVN is poor. Indeed, there is a paucity of gap junctions in the AVN as well as a lack of Cx43 in the compact AVN and inferior nodal extension of the rat, rabbit, and human (27, 197, 198). In contrast, the small-conductance Cx45 is mainly expressed in these regions (119, 120). Expression of Cx43 is also reduced in the transitional zone of the rat, rabbit, and human, but is expressed in the penetrating bundle of the rabbit and human (but not rat) (27, 197, 198). The large-conductance Cx40 is not expressed in the inferior nodal extension of the rat and human, but is expressed in the compact AVN and penetrating bundle (27, 197).

What are the functional consequences of this differential ion channel and gap junction expression? In a series of mathematical simulations in which ionic currents were scaled proportional to mRNA expression, Inada *et al*. showed that computed APs were indeed as expected, with the compact node and inferior nodal extension showing pacemaking activity and APs from these regions also displayed the slowest upstroke velocity (235). In a further series of simulations, it was also demonstrated that slow conduction through the human AVN depends on *both* the low expression of Cx43 and Nav1.5, as simulating just one of these conditions did not fully recapitulate the slow conduction recorded experimentally (150).

AVN Dysfunction

Conduction through the AVN can be pathologically slowed, resulting in heart block. In first-degree heart block, APs still propagate through the AVN, but are slowed, resulting in a prolongation of the P-R interval on the ECG. In second-degree heart block, only some of the APs propagate through the AVN resulting in some P-waves without accompanying QRS complexes. Third-degree heart block is the absence of conduction from the atria to the ventricles. In this case, a ventricular escape rhythm is often present, which can originate from the His-Purkinje system (see below). The incidence of heart block increases with age (271) and with underlying cardiovascular disease, including HF (123), but heart block can also be congenital.

Inherited Syndromes—As in the SAN, mutations in *SCN5A* can also cause AVN dysfunction and heart block. In particular, progressive cardiac conduction defect (PCCD), also called Lev-Lenègre disease, is characterized by progressive dysfunction in impulse propagation through the His-Purkinje system (discussed below) that can result in complete AV block and even sudden death (396). Several loss-of-function mutations in *SCN5A* have been associated with PCCD (58, 426, 534) and these patients may also exhibit BrS or LQTS (272, 396). Watanabe *et al*. recently identified mutations in *SCN1B* (the modulatory β-subunit of Nav1.5) in 3 families with heart block with or without BrS (547). Interestingly, mutations in *KCNJ2* (responsible for Kir2.1 and I_{K1}) have also been associated with sinus bradycardia and heart block (11, 590). This is surprising given that Kir2.1 and I_{K1} are largely absent from both the SAN and AVN. However, heart block may arise due to depolarization and loss of excitability in the working myocardium, thus hindering the spread of impulses from the conduction system to the working myocardium.

Acquired Syndromes—AV block is a common clinical feature of HF and is associated with increased mortality (123), yet very little is known about the structural and ionic remodeling that occur in the AVN as a result of HF. Early histological studies of the AVN of humans with HF documented fibrosis and hypertrophy (367, 466). These findings were confirmed recently in a detailed study of the AVN in failing rat hearts following myocardial infarction (579). Yanni *et al*. found AVN dysfunction accompanied by fibrosis, apoptosis, cellular hypertrophy, and importantly, a downregulation of HCN4 in failing hearts (579). These histological and molecular features likely contribute to slowing of AV conduction and heart block in HF.

His-Purkinje System

Function—The His-Purkinje system represents the ventricular portion of the specialized conduction system and is essential for proper excitation and contraction of the ventricles. The His bundle is the insulated component of the AV conduction axis and, in normal hearts, provides the only AV conduction pathway. The His bundle then bifurcates to form the right and left bundle branches, which run toward the apex of the heart and are insulated from the underlying myocardium by connective tissue sheaths (13). This ensures that the AP is conducted to the apex of the ventricles without first activating the base of the heart. Purkinje networks are formed at the terminations of the bundle branches and are complex three-dimensional structures with both free-running and subendocardial fibers. At specific sites,

the insulating sheath is lost, allowing the Purkinje network to excite the ventricular myocardium (486).

The main function of the His-Purkinje system is to rapidly conduct the AP throughout the ventricles to ensure rapid and efficient ventricular excitation and therefore, coordinated contraction. In addition to rapid conduction of the ventricular AP, the His-Purkinje system can also act as a backup pacemaker in the event of complete heart block. The cells of the Purkinje network are therefore very specialized in order to produce both rapid conduction and, if necessary, a pacemaker potential.

Ionic Mechanisms and Molecular Bases—One factor contributing to fast conduction in the Purkinje fibers is abundant expression of both the large- and intermediate-conductance gap junctions, Cx40 and Cx43 (26, 178, 190). Unlike the SAN and AVN, there is little or no expression of the small-conductance Cx45 (26). Another contributor to fast conduction is the Purkinje AP itself. Unlike the SAN and AVN, the Purkinje AP is not nodal like, but rather has a faster upstroke velocity, higher amplitude, and is longer in duration than the ventricular AP (21, 381, 406). The fast upstroke and large amplitude of the AP contribute to fast conduction. Computer simulations have suggested that differences between the Purkinje and ventricular APs are due to the presence of I_{CaT} in the Purkinje cells but not in the ventricular muscle and increased density of I_{Na} and I_{NaL} and decreased density of I_{CaL}, I_{Kr}, I_{Ks}, and I_{K1} in Purkinje cells (25). For a complete review of ionic currents in Purkinje fibers, see Dun and Boyden (154).

The profile of ion channel expression in Purkinje fibers appears to support the observed AP differences between Purkinje cells and the ventricular myocardium. For example, rabbit Purkinje fibers have increased expression of Nav1.5 mRNA compared to the ventricular myocardium (26), which may contribute to the fast AP upstroke. Rabbit Purkinje fibers also have lower expression of Cav1.2, Kv11.1, Kv7.1, and Kir2.1 mRNA (26), which may contribute to lower densities of I_{CaL}, I_{Kr}, I_{Ks}, and I_{K1}, respectively, and would contribute to the increased APD observed in Purkinje fibers.

Purkinje fibers can also show pacemaking activity, although it is slower than that of the SAN and AVN. Normally, pacemaking in the Purkinje fibers is suppressed by ‘overdrive suppression’, in which the Purkinje fibers are excited during sinus rhythm at frequencies higher than their intrinsic rate. This leads to an increase in $[Na^+]_i$ and enhanced Na^+/K^+ pump activity that causes membrane hyperpolarization and therefore a suppression of diastolic depolarization (75, 263). However, during conditions of AV block, the Purkinje fibers are capable of pacing the ventricles.

Similar to other pacemaking tissues, several ionic currents likely contribute to diastolic depolarization in Purkinje fibers, including I_f (139, 140). Accordingly, robust expression of HCN channels has been documented in the Purkinje fibers of several species, including human (26, 178, 448). There is lower density of I_{K1} (122) in Purkinje fibers that is accompanied by reduced expression of Kir2.1 (26, 178), which likely facilitates pacemaking (25). Purkinje fibers are also susceptible to Ca^{2+} waves occurring as a result of spontaneous Ca^{2+} release from the SR, which leads to Ca^{2+} extrusion via NCX and a net transient inward

current (I_{ti}) that can contribute to diastolic depolarization (73). Thus, it appears as if the Ca^{2+} clock may have a role in pacemaking in Purkinje fibers. This same mechanism, however, also leads to pathological DADs and ectopic beats arising from the Purkinje fibers (71, 73), which have been shown to be significant contributor to arrhythmia in a number of cardiac pathologies (71, 72, 99).

Involvement in Disease—The His-Purkinje system plays a role in the initiation and/or maintenance of ventricular arrhythmias in a number of cardiac pathologies, both acquired and genetic. For example, slowing of conduction in the His-Purkinje network can lead to bundle branch reentry and ventricular tachycardia (VT). The most common form of this arrhythmia, often occurring in patients with dilated cardiomyopathy, involves retrograde activation of the left bundle branch and antegrade activation of the right bundle branch (29). The long AP of Purkinje cells coupled with the voltage- and time-dependent properties of I_{CaL} also make Purkinje fibers susceptible to EADs due to reactivation of I_{CaL} (217, 241). These EADs may initiate *torsade de pointes* arrhythmias in patients with long QT syndrome (41).

As described above, Purkinje cells are also susceptible to DADs and triggered APs due to spontaneous SR Ca^{2+} release (73). Triggered APs arising from the Purkinje fibers are known to be an important initiator of ventricular arrhythmias following myocardial infarction (MI) (240, 473). Accordingly, Boyden and colleagues found that Purkinje cells isolated from the infarct zone of the canine heart 48 hours after MI have 5 times as many spontaneously occurring Ca^{2+} wavelets than do normal Purkinje cells, suggesting a role for Purkinje-mediated DADs in arrhythmias following MI (71, 72). Purkinje-mediated DADs have also been implicated in the initiation of arrhythmias in CPVT. Purkinje cells isolated from a mouse model of CPVT ($RyR2^{R4496C}$) showed high susceptibility to DADs and triggered APs (99). Optical mapping studies of these hearts revealed that focal arrhythmic activity originated from the Purkinje fibers.

Ventricle

Function

Passive filling of blood from the atria into the ventricles occurs while the ventricles are relaxed and the ventricular blood pressure is less than the atrial pressure. Following atrial depolarization, ventricular depolarization can be observed on an ECG as the QRS complex. Ventricular depolarization causes a rise in cytosolic Ca^{2+} which triggers the ventricular muscle to contract (systole), and in turn, pressure rises inside the ventricles causing the atrioventricular valves to close (isovolumetric contraction). Once the pressure inside the ventricles exceeds the arterial pressure, both the pulmonary and aortic valves open, allowing for proper ejection of blood into the pulmonary and systemic circulation. During systole, ventricular repolarization occurs and is observed at the T wave of the ECG. Repolarization allows for removal of cytosolic Ca^{2+} and relaxation of ventricular myocytes (diastole). Collectively, the electrical properties of the ventricles (depolarization and repolarization) can be described on an ECG as the QT interval. Alterations in the duration of the QT interval in disease, typically observed as a prolongation, act as an indication of altered functional properties of ion channels or regulatory proteins during inherited or acquired

diseases (417, 438, 485). The dysfunction of ion channels can lead to a disruption in the normal propagation of the AP waveform ultimately leading to arrhythmia. In particular, prolongation of the QT interval increases the risk for polymorphic ventricular tachyarrhythmias, such as torsades de pointes (TdP) and may ultimately lead to ventricular fibrillation or sudden cardiac death.

Ionic Mechanisms and Molecular Bases

From the AVN, the AP waveform propagates into the ventricular tissue via the conductive cells of the bundle of His and Purkinje fibers. Similar to the atrial AP, ventricular E_m depolarization and the rapid upstroke of the ventricular AP occurs due to the fast activation of voltage dependent Na^+ channels (Nav), which conduct a large, inward I_{Na}. The ventricular AP reaches a more positive E_m (~20 mV *vs.* 0 mV), has a faster upstroke velocity (~372 V/s *vs.* 140 V/s), and has a longer plateau phase than the atrial AP (193, 194). Rapid inactivation of Nav channels and the activation of transient outward Kv channels that conduct outward I_{to} (which is a summation of $I_{to,f}$ and $I_{to,s}$) lead to a partial repolarization of the ventricular E_m known as the 'notch' phase of the ventricular AP (37, 351). L-type Cav channels also activate in response to E_m depolarization, but the time course of activation is slower than Nav channels (Cav channels peak within 20 ms *vs.* Nav channels < 1 ms). When activated, inward I_{CaL} initiates Ca^{2+}-induced Ca^{2+} release from the SR, via cardiac RyRs and increases $[Ca^{2+}]_i$. The rise in $[Ca^{2+}]_i$ generates a contraction as Ca^{2+} binds to the myofilaments of the ventricular myocyte. $[Ca^{2+}]_i$ is extruded in a similar manner as the atria via the electrogenic NCX and Ca^{2+}-ATPase across the plasmalemma and resequestered into the SR via SERCA (47). The delayed rectifier Kv channels are the slowest to activate. These channels activate during the plateau phase to conduct outward I_K predominantly consisting of I_{Kr} and I_{Ks}, which differ in time- and voltage-dependence, regional distribution, and drug sensitivity (331). During the plateau phase, the AP remains depolarized and refractory for hundreds of milliseconds because of the balance between inward I_{CaL} and outward I_K. This phase is essential for the E-C coupling and the duration of the plateau phase is important for normal propagation of the AP waveform. As Cav channels inactivate during the plateau phase, the outward I_K predominates, and repolarization occurs. The inward rectifying I_{K1} (carried by Kir channels) also contributes to repolarization. Kir channels are most permeable at negative E_m and contribute to setting the resting E_m of ventricular myocytes (306, 354). Figure 7 displays a simulated human ventricular AP with corresponding Ca^{2+} transient (CaT) and the major ionic currents that shape the ventricular AP waveform (194).

Species Differences

Many studies of cardiac cellular electrophysiology are performed in non-human species such as mouse, rat, guinea pig, rabbit, or canine. Species-specific differences of the ventricular AP are prevalent in, but not limited to, ion channel or regulatory protein expression, AP repolarization, arrhythmia mechanisms, rate-dependent behaviors, and drug responses (e.g., Figure 8D). These distinct ionic current profiles and AP waveforms correlate with interspecies differences in heart rate (HR) as well (Figure 8A). Smaller animals typically, have high HR such as mouse or rats (~600 or 400 bpm, respectively); whereas, larger mammals have a slower HR such as rabbits or dogs (~200 or 100 bpm, respectively).

Humans have a much slower HR of around 60 bpm. These profound differences need to be kept in mind when interpreting data from various animal species.

One of the most obvious differences in the ventricular AP of mice and rats compared to larger species is the triangular shape and lack of a distinct plateau phase. The ventricular APD of rodents lasts ~35 ms; whereas, the ventricular AP of human, canine, rabbit, and guinea pig display a prominent plateau phase and a long APD lasting hundreds of milliseconds. Differences in expression of repolarizing K^+ channels account mostly for the interspecies heterogeneity of the ventricular AP waveform, but variations in Na^+ and Ca^{2+} channel expression and current densities are also species-specific.

Kv Channels—Of the voltage-gated ion channels, Kv channels are the most diverse superfamily of ion channels and diversity is not restricted to cell type or cell function. Interspecies differences in K^+ channel expression or function in the ventricles have greater impact on AP shape and duration compared to Na^+ or Ca^{2+} channels.

I_{to} activates and inactivates rapidly subsequent to E_m depolarization and is present in most mammalian ventricular myocytes such as rat, mouse, rabbit, canine, and human (22, 44, 56, 183, 218, 244, 298, 491, 512, 550). I_{to} can be dissected into two distinct components, $I_{to,f}$ and $I_{to,s}$ that differ in biophysical properties and conducting α-subunits (359). $I_{to,f}$ and $I_{to,s}$ both activate and inactivate rapidly, but $I_{to,s}$ recovers very slowly from steady-state inactivation compared to $I_{to,f}$. In rat and mouse, I_{to} is large and is the predominant repolarizing K^+-current (206). The high density of I_{to} contributes to early repolarization and lack of plateau phase in the ventricular AP of these species. In humans and canine, I_{to} rapidly, but only partially, repolarizes the membrane during the notch phase of the ventricular AP. As discussed earlier, I_{to} density in human and canine is a reflection of the protein and mRNA expression levels of KChIP2; whereas regional heterogeneities in $I_{to,f}$ in mice and rats is a reflection of the expression levels of Kv4.2 (143, 144, 409, 555). Additionally, in canine and humans, Kv4.3 is the principle α-subunit conducting $I_{to,f}$ and Kv1.4 conducts $I_{to,s}$ (144, 266, 299, 409, 551). In mice and rats, both Kv4.2 and Kv4.3 α-subunits have been shown to conduct $I_{to,f}$, and similarly Kv1.4 protein or mRNA is expressed ventricular myocytes conducting $I_{to,s}$ (172, 203, 204). I_{to} in rabbits mainly consists of $I_{to,s}$ (conducted via Kv1.4), and in guinea pigs, $I_{to,f}$ has not been detected in atrial or ventricular myocytes (166, 170, 236). Indeed, disruption of either *Kcnd2* (encoding Kv4.2) and *Kcnip2* (encoding KChIP2) or *Kcna4* (encoding Kv1.4) in mice eliminates ventricular $I_{to,f}$ and $I_{to,s}$, respectively, and increases the risk of APD prolongation and arrhythmias (32, 204, 268). Decreases in $I_{to,f}$ cause marked alterations in ventricular repolarization that lead to APD prolongation in human and canine HF (349).

The delayed rectifier K^+-current (I_K) is a major outward current responsible for the repolarization of the plateau phase to the resting E_m of the ventricular AP in humans, rabbit, canine, and guinea pig (423). I_K consists of a slowly activating (I_{Ks}) and rapidly activating (I_{Kr}) components that differ in sensitivity to drugs, regional distribution, time-, and voltage-dependent properties (422, 443). I_{Ks} and I_{Kr} were first dissected in guinea pig atrial and ventricular cells and later discovered in human, canine, and rabbit myocytes (227, 286, 300, 418, 511, 512, 514). I_{Kr} is conducted via Kv11.1 α-subunits (otherwise known as the ether-

a-go-go related—ERG1 or hERG for the human protein) and activates rapidly upon depolarization (421). I_{Kr} inactivation occurs at a much faster rate (τ_{inact} < 20 ms) than activation (τ_{act} > 100 ms) and I_{Kr} remains mostly inactivated during the AP upstroke and plateau phase (351, 490). Therefore, during early-repolarization, Kv11.1 channels recover from inactivation and I_{Kr} primarily drives ventricular repolarization during basal conditions. Kv11.1 exists as two splice variants (Kv11.1a and Kv11.1b) and evidence suggests that Kv11.1 interacts with several KCNE β-subunits (KCNE1 and KCNE2) that may be important for native I_{Kr} function (1, 277, 305, 324).

I_{Ks} is conducted by a macromolecular complex that minimally consists of Kv7.1 α-subunits (formerly known as KvLQT1 or KCNQ1) and KCNE1 β-subunits (formerly known as minK or IsK) (31, 420). Co-assembly of Kv7.1 and KCNE1 is critical for native I_{Ks} and KCNE1 increases unitary conductance, positively shifts the voltage dependence of activation, slows activation and deactivation kinetics, and suppresses inactivation of Kv7.1. Kv7.1 can interact with the other KCNE subunits (KCNE2–5) that are expressed at varying levels in the human heart (308, 309). Each KCNE subunit uniquely alters I_{Ks} function when co-expressed in heterologous systems. Co-expression of KCNE2 with Kv7.1 generates small, constitutive currents by increasing the open probability of Kv7.1 at negative or resting E_m and co-expression with KCNE3 generates large, constitutive currents (434, 484). Co-expression of Kv7.1 with KCNE4 or KCNE5 reduces outward current and shifts the voltage dependence of activation to very positive E_m (42). Typically, in most large mammals (such as rabbit, canine, and human), I_{Ks} density has been measured to be much lower than I_{Kr}, and as stated, I_{Kr} plays a prominent role in ventricular repolarization in the absence of β-adrenergic stimulation (245). However, in guinea pig ventricles I_{Ks} plays a greater role in normal repolarization because it is much larger, activation kinetics are faster, and deactivation kinetics are slower than human I_{Ks} (227, 454). Therefore, rabbit and/or canine I_{Ks} more resemble human I_{Ks} and are more suitable to use when studying the function and regulation of I_{Ks} (212, 213, 227, 286, 300, 418). During β-adrenergic stimulation, PKA phosphorylation of the Kv7.1 N-terminus causes an increase of I_{Ks} that is important for normal ventricular AP shortening (321, 525, 532, 533). Mutations associated with congenital arrhythmia syndromes (type 1 long QT syndrome) may disrupt the β-adrenergic upregulation of I_{Ks} and arrhythmogenic events are typically triggered during β-adrenergic stimulation, emphasizing the importance of I_{Ks} to normal ventricular repolarization (35, 214). Additionally, binding of AKAP9 (Yotiao) to the zipper motif on the C-terminus of Kv7.1 is important for recruitment of PKA and protein phosphatases to Kv7.1 and ultimately, β-adrenergic upregulation of I_{Ks}. Congenital mutations within the genes encoding KCNE1 and AKAP9 are also linked to type 5 and type 11 long QT syndromes (LQT5 and LQT11), respectively and can disrupt β-adrenergic regulation of I_{Ks} (104, 462).

The interspecies differences of the contribution of I_{Kr} and I_{Ks} to ventricular repolarization can also be observed selective drug block. Experimental studies in isolated ventricular myocytes and computational simulations of the ventricular AP show that complete block of I_{Ks} does not significantly alter APD or AP morphology in humans or dog (194, 247, 416). However, blockage of I_{Kr} in humans or dog does cause APD prolongation and alters repolarization kinetics in human myocytes (Figure 8D). This coincides with the assumption that human I_{Ks} contributes minimally to normal repolarization, but is critical to APD

shortening during β-adrenergic stimulation. Furthermore, when the repolarization reserve is compromised (by drugs or diseases that reduce I_{Kr} or I_{K1}) I_{Ks} may play a more prominent role in preventing ventricular APD prolongation. Interestingly, computational simulations predict that blocking I_{Kr} prolongs the human ventricular APD and when blocking both I_{Kr} and I_{Ks} the prolongation is even greater (194, 248). Due to the unusually large contribution of I_{Ks} to normal repolarization in guinea pig, blocking I_{Ks} without β-adrenergic stimulation significantly prolongs the ventricular APD (Figure 8D); whereas in human, dog, and rabbit no prolongation occurs (68, 194, 247, 282, 511, 520).

In adult rat and mouse, I_{Kr} and I_{Ks} are mostly immeasurable (246, 568). Several delayed rectifier K^+-currents have been identified in adult mouse or rat ventricular myocytes ($I_{K,slow1}$, $I_{K,slow2}$, I_{ss}) (22, 216, 567). Rodent ventricular I_{ss} is a steady-state non-inactivating outward K^+-current that resembles human atrial I_{Kur} and is inhibited by high concentrations of 4-AP (54). We recently incorporated rodent delayed rectifier K^+-currents, rodent I_{to}, and rodent I_{K1} into a computational model of a rabbit ventricular AP and showed the progression of how repolarizing K^+-currents alter the AP waveform (339). Altering I_{to} voltage-dependence and kinetics of activation and inactivation to resemble current properties in mice shortens the AP plateau and APD (Figure 8B–C). Implementing the mouse-specific $I_{K,slow1}$, $I_{K,slow2}$, and I_{ss} shortened the APD further and eliminated the AP plateau (Figure 8B–C). Lastly, I_{K1} was reduced to a similar magnitude observed in isolated mouse myocytes and caused prolongation of the late repolarization phase and AP triangulation (Figure 8B–C). This transformation of a rabbit-like ventricular AP to an AP that is more representative of a mouse or rat suggests that the species-dependent AP differences are largely accounted for by the heterogeneity of repolarizing K^+-currents.

Inward Rectifying Channels—I_{K1} is important for late phase repolarization of the ventricular AP (306). I_{K1} is also the primary conducting current during diastole that sets the resting E_m (351). Indeed, I_{K1} is present in ventricular myocytes from most species (mouse, rat, canine, rabbit, guinea pig, and human) and I_{K1} is conducted through Kir2.x α-subunits (153, 302, 354, 355, 450, 474, 512). Kir α-subunits differ from Kv α-subunits in that they only consist of two transmembrane segments (Kv α-subunits have six), are voltage-independent, conduct large, inward K^+-current at E_m more negative than E_K, and conduct small, outward K^+-current at E_m more positive than E_K (354). In mice, there is evidence suggesting two proteins conduct I_{K1}. Disruption of the genes that encode Kir2.1 and Kir2.2 (*KCNJ2* and *KCNJ12*, respectively) caused a reduction in I_{K1} compared to wild-type mouse ventricular myocytes (587, 588). In humans, Kir2.1 is generally considered the main α-subunit underlying I_{K1} with predominant expression in the ventricles compared to the atria (136, 178, 543). A recent study comparing canine and human ventricular myocytes showed that Kir2.1 mRNA expression was significantly higher in canine than human compared to other Kir2.x isoforms. Additionally, Kir2.1–4 mRNA or protein was indeed present, and Kir2.1 and Kir2.3 mRNA or protein were expressed at similar levels in myocytes isolated from human (248). These data suggest the possibility that heteromeric Kir2.x channels may conduct I_{K1} in humans (432). Mutations in the gene, *KCNJ2*, encoding Kir2.1 cause a dominant-negative effect on I_{K1} and are linked to congenital arrhythmia syndromes such as Andersen-Tawil syndrome (type 7 long QT syndrome) which may lead to periodic paralysis,

ventricular arrhythmias, and dysmorphic features (476, 488). To date, no mutations in genes encoding other Kir2.x α-subunits have been reported, supporting the predominant role Kir2.1 has in conducting human I_{K1}.

I_{KATP} is another inward rectifier K^+-current important for the ventricular AP and is important for cardioprotection in ischemic conditions (351, 425, 469). mRNA of two isoforms, Kir6.1 and Kir6.2, are expressed in human ventricles and can bind to two ATP-binding cassette proteins, SUR1 and SUR2. Kir6.2 is most likely more abundant, and is associated with SUR2A (92, 173, 178). Kir6.x α-subunits conduct I_{KATP} and are typically closed in normal conditions due to high levels of intracellular ATP in normally functioning ventricular tissue. The channels open during metabolic insult subsequent to increased cardiac output, hypoxia, or ischemia (92, 237, 599). Increasing I_{KATP} acts to shorten the ventricular APD to reduce calcium entry and reduce contractility, which ultimately decreases energy consumption protecting the cell. Opening of Kir6.x channels is thought to be cardioprotective due to ischemic preconditioning, which is lost in Kir6.2 knockout mice. The Kir6.2 knockout mice were also more vulnerable to ventricular arrhythmia and sudden cardiac death when exposed to decompensated HF, exercise stress, or hemodynamic stress (253, 303, 468, 571). Additional studies revealed that Kir6.1 or SUR1 knockout mice do not affect ventricular I_{KATP}, but atrial I_{KATP} was abolished (442). In dogs, specific blockade of Kir6.x channels prevented ischemic preconditioning as well. Together, these results suggest the importance of I_{KATP} and Kir6.2 has in ischemic preconditioning in several species.

Nav Channels—Conducting I_{Na}, the principal Nav α-subunit expressed in mammalian ventricular myocytes is Nav1.5, encoded by *SCN5A* (584). Although, Nav1.5 is blocked by tetrodotoxin (TTX) at μM concentrations, it is considered TTX-resistant compared to other Nav subunits that are blocked by nM concentrations of TTX. Nav1.5 has a single amino acid change from phenylalanine to cysteine in the pore region of domain I that causes a large reduction in TTX sensitivity (424). In functional studies, Nav1.5 are found roughly homogenously distributed in the t-tubules and external sarcolemma, whereas non-cardiac Nav isoforms (whose role is still poorly understood) are more concentrated at the t-tubules (80). Experimental results using immunocytochemistry in isolated rat ventricular myocytes revealed that Nav channels are localized at the sarcolemma and t-tubule, and interestingly at intercalated disks (117). These data suggest that different pools of Nav1.5 may serve a different functional purpose in different regions of the myocyte (i.e. channels at intercalated disks may be important for conduction or channels at t-tubules may be important for sarcolemma depolarization). Protein or mRNA of several other TTX-sensitive Nav α-subunits (Nav1.1, Nav1.2, Nav1.3, Nav1.4, Nav1.6, and Nav2.1) have also been identified in ventricular myocytes of human, mouse, rat, and rabbit, but a clear role of these Nav channels has not been established (178, 267, 316, 351, 382, 430). A study comparing RNA isolated from whole hearts showed that mouse and rat hearts expressed higher levels TTX-sensitive Nav channels overall compared to humans (61, 137, 598). The protein sequences of the different Nav channels are highly conserved across species implying the channel structure is likely also conserved.

Several mutations in *SCN5A* have been linked to type 3 long QT syndrome (LQT3), and typically cause an enhancement in I_{NaL} (540). Normally, up to 99% of Nav channels are

inactivated within a few milliseconds, but a small fraction of Nav channels may remain activated during the plateau phase and is defined as I_{NaL}. In situations where I_{NaL} is increased (e.g. LQT3 or HF), ventricular APD prolongation occurs and increases the propensity to ventricular arrhythmia. Recently, genome- and phenome-wide association studies (GWAS and PheWAS, respectively) also suggest that single nucleotide polymorphisms (SNP) at chromosome 3 *SCN5A-SCN10A* loci associate with patient QRS duration and subsequent ventricular and atrial arrhythmia susceptibility. Interestingly, SNPs in *SCN10A* (encoding the neuronal TTX-resistant Nav1.8 α-subunit) specifically associated with AF (405) and is consistent with a previous study of a large population that associated *SCN10A* SNPs with QRS duration and propensity for cardiac arrhythmia (100).

Cav Channels—The predominant Ca^{2+}-current in the mammalian ventricles is I_{CaL} and is conducted via *CACNA1C*-encoded Cav1.2 α1-subunits (457). I_{CaL} is inactivated by both Ca^{2+}-dependent (CDI) and voltage-dependent (VDI) mechanisms during the ventricular plateau phase (255). In the ventricular myocyte (and all other cardiac myocytes), Cav1.2 exists as a macromolecular complex associated with ancillary subunits such as β2a, α2δ, and γ (23, 118, 234, 380). Therefore, in heterologous systems, Cav1.2 expression alone does not recapitulate native-like I_{CaL}, but rather requires co-expression with ancillary subunits, specifically β2a. I_{CaL} activates at more depolarized E_m than the atrial specific I_{CaT} (when E_m is more positive than −20 mV compared to −50mV, respectively) and undergoes voltage- and Ca^{2+}-dependent inactivation more slowly (38, 91, 97, 98, 378). Therefore, L-type Ca^{2+}-channels and T-type Ca^{2+}-channels have been referred to as high voltage-activated and low voltage-activated, respectively. The specific biophysical properties of I_{CaL} are important for triggering SR Ca^{2+}-release and can influence repolarization and ventricular APD. Mature human ventricular myocytes almost exclusively express Cav1.2 (178). Contrary to these findings, studies reported the presence of I_{CaT} and/or Cav3.1 mRNA in neonatal mouse, rat, and rabbit ventricular myocytes (379, 553, 554). Furthermore, I_{CaT} and Cav3.1 mRNA is re-expressed in feline or rat disease models of ventricular hypertrophy (320, 362).

CACNA1C mutations (G406R and G402R) are linked to the extremely rare Timothy syndrome (formerly LQT8) and are associated with extreme QT prolongation, developmental delay, syndactyly, immune deficiency, cognitive deficits, and ventricular fibrillation.(461) Both mutations cause a gain-of-function phenotype by disrupting Cav1.2 inactivation that leads to an increase in I_{CaL} and ventricular APD prolongation. In a transgenic mouse model of Timothy syndrome, I_{CaL} was increased, ventricular APD_{90} was prolonged, $[Ca^{2+}]_i$ was elevated, and there was an increased frequency of EAD- and DAD-induced arrhythmogenic events (110). These observed functional changes in I_{CaL} are similar to the HF and CaMKII effects on I_{CaL} discussed below.

Atrioventricular Differences

Ventricular myocytes maintain a slightly more hyperpolarized resting E_m (~−85 mV) compared to atrial myocytes (~−80 mV) and the plateau phase of a ventricular myocyte AP reaches a more depolarized E_m (~20 mV) (406, 430, 544). The ventricular AP plateau phase is also longer, V_{MAX} of the AP upstroke is faster, and repolarization occurs at a faster rate

than the atrial AP. Ventricular myocytes are also larger and have a greater surface:volume ratio than atrial myocytes due to a higher density of t-tubules.

The hyperpolarized resting E_m is likely due to the larger I_{K1} measured and higher expression of Kir2.1 mRNA (encoded by *KCNJ2*) in ventricular myocytes (136, 161, 178, 183, 543). In the atria, the predominant I_{K1} conducting α-subunit is Kir2.3 (encoded by *KCNJ4*) (178, 430). Ventricular $I_{to,s}$ is larger in humans, which is consistent with a high ventricular expression of Kv1.4 and KChIP2 mRNA (178). However, $I_{to,f}$ is less and the V½ of activation and inactivation are more positive in human ventricles compared to atrial tissue. These observations correspond to a lower expression of Kv4.3 mRNA and protein in human ventricles (9, 178). I_{Kur} and $I_{K,Ach}$ and their respective transcripts, Kv1.5 and Kir3.1 mRNA, are almost absent in human ventricular myocytes; whereas, both K^+ currents contribute significantly to the atrial AP (135, 151, 161, 178, 430, 542, 586). However, a mutation in *KCNJ5* (encoding Kir3.4) was recently linked to LQT13 in one family and Western blot analysis revealed the presence of Kir3.4 (and Kir3.1) in human ventricular tissue suggesting the role of $I_{K,ACh}$ may be underestimated in ventricles (576). Additionally, I_{Kr} and I_{Ks} density and the mRNA expression are similar in human atrial and ventricular myocytes (178, 431).

The human ventricular AP morphology has a longer plateau phase due to an overall lower density of K^+-currents activated during the notch phase (i.e. smaller I_{to} and I_{Kur} during early repolarization). As ventricular repolarization occurs later in the AP time-course, more I_{Kr} recovers from inactivation and contributes to a fast rate of repolarization compared to the atrium.

The principle Na channel α-subunit that conducts I_{Na} in both atrial and ventricular myocytes is Nav1.5 (encoded by *SCN5A*) (178, 181, 430, 539). Studies using immunohistochemistry in rats suggested that Nav1.5 is expressed predominantly in intercalated discs and also in lateral membranes and the T-tubules (407). Importantly, differences in drug sensitivity and inactivation properties are present between I_{Na} from either chamber and may be related to a higher availability of I_{Na} or, to a lesser extent, a lower expression of the ancillary subunit, β1, in the ventricles (88, 178). β1 shifts the V½ of inactivation of Nav1.5 to more positive E_m (137). A more convincing argument on why inactivated state-dependent Na^+ channel blocker sensitivity is higher for atrial I_{Na} is due to a depolarized resting E_m. As a result, this increases the probability of atrial Nav1.5 channels to be in an inactivated state at rest. Therefore, inactivated state-dependent Na^+ channel blockers have a higher propensity to block atrial I_{Na} *vs.* ventricular I_{Na}; whereas, open state-dependent Na^+ channel blockers are not atrial selective (89).

Functional I_{CaL} is present in atrial and ventricular myocytes and is conducted by Cav1.2 (encoded by *CACNA1C)* (457). In humans, mRNA expression of Cav1.2 is the highest of Cav channels in the atria and ventricles (178, 430). The mRNA of a secondary L-type Cav channel, Cav1.3, is expressed at higher levels in atrial cells compared to ventricular cells of human, mouse, and rabbit myocytes, although overall expression of Cav1.3 is low compared to Cav1.2 (178, 318, 319, 399). However, the contribution of Cav1.3 to the AP is greater in the SAN and AVN (see SAN and AVN sections above). In normal mammalian ventricular

myocytes, I_{CaT} is almost undetectable, but I_{CaT} is present in canine, feline, guinea pig, and rat atrial myocytes (290, 351, 430). Additionally, the mRNA expression of the I_{CaT} conducting α-subunit, Cav3.1, is very low in humans, yet expression in ventricular myocytes is lower than in atrial myocytes (178). A Cav channel ancillary subunit, α2δ2, which modulates both I_{CaL} and I_{CaT} was found to be expressed higher in human atrial myocytes than ventricular myocytes, suggesting an explanation for chamber-specific functional properties of these currents (178, 179).

Protein and mRNA expression of NCX1 are higher in human ventricular myocytes *vs.* atrial (178, 537). Subsequent studies that reduced maximal I_{NCX} by 30% in a human atrial computational model from an existing ventricular model predicted an increased fraction of NCX active during the cardiac cycle (193, 194). This result is likely due to the atrial AP morphology causing a larger I_{CaL} and slightly larger CaT that favors inward I_{NCX}. These simulations emphasize how the electrogenicity of NCX is sensitive to both E_m, $[Ca^{2+}]_i$, and $[Na^+]_i$.

Gap junction hemichannels allow for direct electrical and metabolic coupling between adjacent cardiac myocytes (57). While both Cx40 (encoded by *GJA5*) and Cx43 (encoded by *GJA1*) protein and mRNA are highly expressed in atrial myocytes, Cx43 is the predominant ventricular connexin (178, 254, 483, 526). Expression of Cx40 is much stronger in atrial *vs.* ventricular tissue in humans, dogs, rabbits, guinea pigs, and mice (178, 254, 319, 430, 516, 526). Additionally, in humans, Cx45 mRNA was expressed at low levels compared to Cx40 and Cx43 in the atria and ventricles, respectively (178). The importance of Cx43 for ventricular conduction was observed in several studies that involved heterozygous or homozygous knockouts of Cx43 in mice. Both studies reported minimal effects in the atria; whereas, ventricular conduction was severely impaired highlighting the predominant role Cx43 has in the ventricles (483, 502).

SK channels are voltage-independent and have been identified to conduct an apamin-sensitive K^+ current predominantly in normal human and mouse atrial myocytes compared to ventricular myocytes (569). Specifically, SK2 mRNA (*KCNN2*) expression was lower in human ventricular myocardium compared to the atria (161). In mice, SK1 and SK2 mRNA are expressed higher in the atria; whereas, SK3 mRNA is equally expressed in the atria and ventricles (495). I_{SK} is important for late phase atrial repolarization and inhibition of I_{SK} can prolong the APD. In the rat, rabbit, dog, and human, I_{SK} does not have a significant contribution to ventricular repolarization (115, 311, 347). Subsequent studies have provided a possible role for I_{KAS} in ventricular repolarization, but only in pathogenic situations when other K^+ channels are downregulated (3). I_{SK} is upregulated in diseased myocytes from rabbit, rat, and human and may be important in human arrhythmogenesis (102, 115, 202, 229).

Understanding critical differences in ionic current densities, ion channel expression, drug sensitivities, or voltage- and time-dependent properties between ventricular and atrial myocytes are important for chamber specificity of anti-arrhythmic drug therapy. Utilization of a chamber specific approach for therapeutic intervention may aid in the prevention or reoccurrence of specific ventricular or atrial arrhythmias.

Ventricular Regional Differences

Regional heterogeneity of the ventricular AP morphology has been thoroughly studied. AP differences exist when comparing the transmural heterogeneity across the ventricular wall, between the left and right chambers of the ventricles, and from the apical region to the base. Without electrical coupling via gap junctions, these differences are exacerbated, and the intrinsic AP of an isolated cell is due to the unique expression profile and function of ion channels and regulatory proteins of that particular cell (70, 556).

Transmural Differences—Three distinct AP waveforms have been distinguished from three predominant cell types contributing to the transmural heterogeneity of ventricular repolarization: the epicardial, midmyocardial (M-cells), and endocardial myocytes. The most notable differences among these three cell types are the large appearance of a ‘spike and dome’ (large notch phase) in the epicardical myocytes, and the M-cells having a prolonged APD by ~100 ms compared to epi- and endocardial myocytes (20, 573). The APD of epicardial myocytes is shorter than endocardial myocytes; whereas, endocardial myocytes have a less pronounced notch phase (452). The transmural differences throughout the APD of epicardial, M-cells, and endocardial myocytes are important for determining the duration and shape of the T-wave on an ECG (239, 572). Drugs or diseases that selectively reduce K^+-currents (I_{to}, I_{Kr}, or I_{Ks}) or increase I_{Na} or I_{CaL} typically cause a greater APD prolongation of the M-cell than epi- or endocardial myocytes, in turn increasing the transmural heterogeneity of repolarization. The amplified transmural APD heterogeneity may culminate into reentrant arrhythmias (17). Therefore, abnormalities in transmural repolarization can be distinguished on an ECG and can be used for prognosis and treatment (15, 16, 572).

The distinct notch phase in the AP waveform of epicardial myocytes has mainly been attributed to a large I_{to} recorded from human, canine, feline, rabbit, and rat myocytes (116, 166, 176, 299, 301, 346, 551). The ancillary subunit, KChIP2, modifies the function of Kv4.3 α-subunits, which conduct canine and human I_{to} (10, 144, 249). KChIP2 mRNA expression is highest in epicardial myocytes and lowest in endocardial myocytes (178, 409, 430). Kv4.3 transmural expression is not different, but only the KChIP2 expression correlates with the $I_{to,f}$ gradient and prominence of the notch phase (epi > M-cells > endo). Kv4.2 mRNA has been shown to be minimally expressed in human and canine ventricular myocytes, but is important for I_{to} generation in mouse and rats (143, 144, 178, 409, 430, 594).

Another important finding is that I_{Ks} recorded from M-cells is lower than that recorded from epi- or endocardial canine myocytes (300, 301). I_{Ks} is important for normal repolarization of the ventricular AP and the reduction in I_{Ks} contributes to the prolonged APD of M-cells. The I_{Ks} macromolecular channel complex minimally consists of Kv7.1 α-subunit and KCNE1 β-subunit (formerly known as minK), encoded by *KCNQ1* and *KCNE1*, respectively (31, 420). *KCNQ1* mRNA was found to be highest in left ventricular epicardium *vs.* endocardium and M-cells, and other studies have suggested that *KCNE1* expression is unchanged transmurally (178, 377, 430). Additionally, a dominant negative isoform of Kv7.1, encoded by *KCNQ1b*, was found expressed at high levels in M-cells, which could

explain the reduction of I_{Ks} (377). Drugs that specifically modulate *KCNQ1* splicing have been implicated in reducing *KCNQ1b* and shortening the APD in canine M-cell (280). These findings could have great impact in treating disease that involves remodeling of I_{Ks} or other repolarizing currents. In general, the more prominent I_{Ks} in epi- and endocardial myocytes is protective against EADs and stimulus reentry compared to M-cells (86). There is a lack of clear evidence of transmural differences in the human or canine ventricles for I_{Kr} and I_{K1}, also important for ventricular repolarization, (15, 70, 300, 471).

Transmural differences in I_{Na} have been identified, whereas recordings performed in canine M-cells show that I_{NaL} in increased compared to epi- and endocardial myocytes, but these findings were not observed in guinea pig myocytes (600). A larger I_{NaL} could contribute to the longer APD observed in M-cells. Several studies have also suggested that there is a larger I_{Na} present or higher levels of Nav1.5 and β1 mRNA in endocardial myocytes compared to epicardial myocytes isolated from rat, canines or humans and this coincides to a faster upstroke velocity (V_{MAX}) of the endocardial AP (178, 408, 471). Another depolarizing current that is found to be larger in canine M-cells than epi- or endocardial myocytes is the sodium-calcium exchange current (I_{NCX}) and the increased I_{NCX} may contribute to the lengthened APD of M-cells (601).

Several studies suggest that I_{CaL} is not different from canine epicardial, M-cells, or endocardial myocytes isolated from the left ventricle (30, 121). However, one study did suggest that canine endocardial myocytes have larger I_{CaL} and the functional properties of I_{CaL} differ in all three regions (535). Interestingly, in human Cav1.2 mRNA expression is highest in epicardial myocytes along with the transcripts for several important calcium handling proteins (RyR2, NCX1, SERCA2, calcineurin-α, and CALM3) (175, 178, 189, 293, 392, 536, 566). The high expression of calcium handling proteins in human or canine epicardial myocytes results in a faster onset and time-to-peak of contraction, and a more rapid relaxation than endocardial myocytes (121, 175). Cx43 protein, the main connexin expressed in ventricular myocytes, is expressed at higher levels in M-cells or endocardial cells than epicardial cells in dogs and mice, but there are no differences in humans or rats (70, 385, 570). Surprisingly, the atrial-specific Cx40 mRNA had a higher expression in left endocardium *vs.* left epicardium, although overall expression was less than Cx43 mRNA in the ventricles (178).

Left vs. Right Ventricle—The transmural AP gradient exists across the three layers of myocardium in the left and right ventricle, but overall, the left ventricular APD is longer compared to the right ventricular APD (70, 285, 346). The shorter APD of right ventricular myocytes has been attributed to a greater I_{to} recorded from isolated canine and human right ventricular myocytes (138, 524). Indeed, mRNA and protein expression of KChIP2, a protein that modifies Kv4.3 α-subunits and increases $I_{to,f}$ is expressed at higher levels in human and canine right ventricular myocytes compared to left ventricular myocytes (70, 138, 524). Canine expression of KChIP2 mRNA and protein closely match the differences of $I_{to,f}$ in left and right ventricular myocytes and the transmural gradient of I_{to} (400). Human and canine differences in density of I_{to} tend to be controlled by the variable expression of KChIP2 and not the expression of Kv4.3. However, in rat and mouse, Kv4.2 and Kv4.3 α-

subunits conduct $I_{to,f}$, and differential expression of Kv4.2 mRNA and protein correlate with regional differences in I_{to} (144, 249, 409, 555).

Another contributing factor to the shorter APD of the right ventricles is the density of I_{Ks}. Like I_{to}, I_{Ks} measured from canine myocytes was larger in M-cells isolated from the right ventricle compared to the left (524). The larger I_{Ks} correlates with larger protein expression of KCNE1 in right ventricular myocytes as well (401). KCNE1 expression modulates the I_{Ks} conducting Kv7.1 α-subunit by slowing the time course of activation and deactivation, suppressing inactivation, positively shifting the voltage dependence of activation, and increasing the single unitary conductance (31, 420). No differences in other repolarizing K^+-currents such as I_{Kr} or I_{K1} have been observed between left or right ventricular myocytes (524). In tissue from the right ventricular septum of dog, a higher expression of KChIP2, Kv7.1, and NCX1 mRNA was reported, and the APD of myocytes from the right ventricular septum was shorter than the left as expected (400).

AP waveform conduction velocity in the ventricles relies on the availability of Nav1.5 channels and gap junction coupling via Cx43 (556). Although, differences in expression of Nav1.5 and Cx43 in the left or right ventricle have not been demonstrated, pharmacological block or reduced expression of Nav1.5 or Cx43 in mice slows conduction velocity more in the right *vs.* left ventricle (506, 507). These observations depict how the effects of regional heterogeneity may increase susceptibility to arrhythmogenesis. Differences in the origin of arrhythmia also exist; for example, in BrS, ventricular arrhythmias are initiated in the right ventricular outflow tract by either conduction slowing or unidirectional impulse block (177, 337). Congenital BrS is linked to mutations in *SCN5A* in up to an estimated 30% of all cases, and these mutations decrease the function of Nav1.5 by reducing cell surface expression, shifting the voltage- and time-dependence of inactivation, delaying recovery of inactivation, or accelerating the time-course of inactivation (18, 107). Reduction of Nav1.5 function leads to a decrease in I_{Na} and causes an increase in the notch phase and loss of AP dome of epicardial myocytes. As a result, transmural dispersion of repolarization increases and ultimately, increases the risk for reentrant arrhythmias and incidence of sudden cardiac death (269, 444).

Apex vs. Base—Apico-basal heterogeneity was first discovered in canine myocytes, whereby cells isolated from the apex had a shorter APD than cells isolated from the base of the left ventricular wall (472). Larger I_{to} and I_{Ks} correlated with the shorter APD in apical myocytes compared to basal. The same study showed that the increases in repolarizing currents are most likely a result of higher protein expression of KChIP2 (I_{to}), Kv7.1 (I_{Ks}), and KCNE1 (I_{Ks}) in both human and canine apical myocytes than basal myocytes (472). No apico-basal differences were observed in densities of I_{CaL}, I_{K1}, or I_{Kr}, and the protein expression of the corresponding pore forming α-subunits (Cav1.2, Kir2.1, and Kv11.1) and β-subunits (KCNE2). In contrast, the APD of rabbit, ferret, and rat apical myocytes have been shown to be longer than basal myocytes (70, 78, 111, 548). In rabbit, I_{Kr} is paradoxically larger in apical myocytes, but I_{Ks} is much smaller in apical myocytes compared to basal. However, this study did not take into account apico-basal differences of I_{to}.

Ventricular Arrhythmia and Disease

Ventricular arrhythmia can describe a broad range of abnormal electrical activity that may lead to ventricular tachycardias and can culminate in ventricular fibrillation and sudden cardiac death. The mechanisms of arrhythmia in the ventricles are similar to the atria and are referenced in the atrial section above (see section *Atrial Fibrillation: Mechanisms and Ionic Remodeling* and Figure 5). Typically, tachycardias are dependent on a triggering stimulus (e.g., ectopic foci) and a substrate for sustainability (e.g., reentrant loop). Alterations in ion channel function or expression can disrupt the morphology of the AP waveform, which can ultimately lead to abnormal propagation of the heart's electrical impulse and arrhythmia. Ion channel dysfunction or expression remodeling can occur in diseases that can be inherited (LQTS, BrS, CPVT, etc.) or acquired (HF, MI, etc.).

Over the past several years, molecular and biophysical studies have linked a genotype-phenotype correlation between several multigenerational inherited cardiac arrhythmia syndromes and mutations within genes encoding ion channels or ion channel regulatory proteins. These arrhythmia syndromes (otherwise known as 'channelopathies') include LQTS, SQTS, BrS, CPVT, familial lone AF, and familial bradycardia. Table 2 displays inherited ventricular arrhythmia syndromes and the association of each disease with a specific gene and the specific cardiac current affected. Of note, mutations in different ion channels often lead to the same pathological phenotype. For example, mutations in genes encoding Kv, Nav, and Cav channels can all lead to AP prolongation and manifest as LQTS. Similarly, various mutations are now being linked to CPVT, including mutations in *RyR2*, *CASQ2*, *CALM1*, and *KCNJ2* (Kir2.1). Thus, there is substantial overlap in the many genotypes that can all lead to a similar disease phenotype.

HF is one of the leading causes of death in the United States each year and the prevalence continues to increase with an aging population (186). HF is associated with deficiencies in cardiac function that is a result of structural and electrophysiological remodeling of the cardiac tissue. Remodeling significantly increases the risk of arrhythmia in HF patients, and nearly half of deaths reported in HF patients are a result of ventricular arrhythmias (158, 262). Remodeling of cardiac electrophysiology is due to alterations in expression and function of ion channel and/or ion channel regulatory proteins. A common observation in failing ventricular myocytes isolated from humans or animal models of HF is the prolongation of the ventricular APD and a higher incidence of EADs or DADs compared to control cells (5, 56, 250, 410). These observations may be a direct result in the ventricular remodeling of ion channels, which increases the likelihood of arrhythmia and sudden cardiac death. In the following sections, we will discuss the underlying molecular and/or biophysical mechanism of ion channel remodeling in the ventricular myocyte during HF.

Nav Channels—HF-induced abnormalities may affect both the expression and post-translational modifications of Nav1.5 and contribute to ventricular APD prolongation. Several studies have suggested that peak I_{Na} is reduced in HF (270, 349, 499, 504, 596). Other studies show an increase in I_{NaL} in both tachypaced HF-induced canine and human HF ventricular myocytes (499–501, 504). Similar results were observed in HF-induced mice by transgenic overexpression of CaMKIIδC, whereby I_{NaL} was markedly increased (315,

527). Together, these observations could be a result of post-translational modification of Nav1.5 by CaMKII phosphorylation. A decrease in peak I_{Na} may lead to conduction slowing or ventricular arrhythmias via stimulus reentry; whereas, an increase in I_{NaL} may alter $[Na^+]_i$ or $[Ca^{2+}]_i$ homeostasis, delay repolarization, cause ventricular APD prolongation, and increase the risk of ventricular arrhythmias (215). Furthermore, CaMKII expression and activation is increased in HF, and inhibition of CaMKII is protective of HF by reducing pathological signaling and arrhythmias (12, 221, 591). These arrhythmogenic mechanisms are similar to observed biophysical phenotypes associated with congenital arrhythmia syndromes (LQT3 or BrS) involving mutations in *SCN5A* (45).

One study reported no alterations in mRNA expression of Nav1.5 and β1 in samples from human or canine HF ventricular myocytes compared to control (504). However, a more recent study suggested that in human HF, non-functional truncated Nav1.5 mRNA splice variants are increased, but the role of this splice variant remains unknown (180, 446).

Cav Channels—In most human studies of isolated ventricular HF myocytes, no changes in I_{CaL} have been observed, but there are reports of decreased I_{CaL} in HF (4, 50, 349, 384). Several studies involving tachypaced HF-induced dogs, tachypaced HF-induced rabbits, or pressure/volume overload HF-induced rabbits have also yielded no decrease in I_{CaL}, albeit, strong reductions in contractile force and Ca^{2+}-transients (250, 365, 387, 413). Furthermore, increases in I_{CaL} subsequent to β-adrenergic stimulation were blunted in ventricular HF myocytes (250, 341, 413). Other studies using single channel recordings have suggested that although, the number of Cav1.2 channels at the cell membrane is reduced in human HF, overall I_{CaL} density is unchanged due to an increased open probability (108, 209, 433). An increase in open probability likely correlates to increased phosphorylation of Cav1.2. Indeed, CaMKII (and PKA) phosphorylation enhances peak I_{CaL} and slows inactivation, which results in an increase in Ca^{2+} influx (155, 585). Together, the increased open probability of Cav1.2, increased Ca^{2+} entry, and increased SR Ca^{2+} release leads to higher $[Ca^{2+}]_i$ in HF and may lead to DADs via I_{NCX} removal of Ca^{2+}. Rabbit ventricular AP simulations suggest that impairment of Ca^{2+}-dependent inactivation (CDI) of I_{CaL} can lead to development of EADs during a prolonged ventricular APD by a similar mechanism (340). Ventricular APD prolongation alone, without the HF-induced alterations of I_{CaL}, may also trigger arrhythmogenic EADs by increasing the probability of Cav1.2 channels to reactivate (288, 363, 444).

Several studies have also attempted to determine the molecular regulation in Cav1.2 expression and alterations of I_{CaL} density in HF. Two studies reported no change in Cav1.2 mRNA expression in human HF ventricular myocytes (433, 440). Other studies reported alternative splicing events; whereas, Cav1.2 mRNA underwent isoform switching and the regulatory subunit, β3a, was truncated (233, 574).

Kv Channels—As previously stated, a typical feature of isolated ventricular myocytes of HF humans or animal models is APD prolongation and increased EAD susceptibility (4, 349, 444). These common findings are sometimes a direct result of reductions in the repolarization reserve, which are also observed in several forms of congenital arrhythmia syndromes such as type 1 or type 2 LQTS (LQT1 or LQT2). Indeed, HF-induced

remodeling may cause a reduction in several repolarizing K^+-currents. The most consistent change to ionic currents during HF is the downregulation of I_{to}. A reduction of I_{to} has been reported in isolated ventricular myocytes from human HF patients, tachypaced HF-induced dogs, tachypaced HF-induced rabbits, and pressure/volume overload HF-induced rabbits (56, 249, 250, 345, 388, 413, 492, 493). The reduction in I_{to} corresponds to decrease in protein and mRNA expression of Kv4.3 and no change in I_{to} voltage-dependence or kinetics (6, 249, 345, 410, 493, 565, 597). The majority of these studies also conclude that KChIP2 expression is unchanged in HF ruling out KChIP2 regulation of Kv4.3 as a cause of decreased I_{to}. In tachypaced HF-induced dogs, reduced I_{to} was directly linked to increases in CaMKII activation and calcineurin/NFAT signaling. This led to a reduced expression of Kv4.3 mRNA and protein (565). Although, I_{to} is important for the notch phase or early repolarization in the ventricular AP, downregulation of I_{to} may contribute to APD prolongation. Additionally, computational simulations of a rabbit ventricular AP that incorporate CaMKII-dependent effects on I_{to} together with I_{to} heterogeneity can exacerbate transmural dispersion of repolarization, increasing the vulnerability to reentrant arrhythmias (195).

The delayed rectifier K^+-currents, I_{Kr} and I_{Ks}, play a key role to late phase ventricular repolarization and have a direct effect on the ventricular APD. However, there is more ambiguity in whether or not I_{Kr} and I_{Ks} are reduced in HF. Downregulation of I_{Kr} and I_{Ks} has been shown from isolated ventricular myocytes of tachypaced HF-induced rabbits in one study, but only I_{Ks} has been reported to be decreased from tachypaced HF-induced canine myocytes (287, 492). In humans, I_{Ks} was decreased in HF myocytes isolated from the right ventricle; whereas, I_{Kr} was unchanged (288). Interestingly, a recent study specifically blocked I_{Kr} in isolated non-failing or HF left ventricular wedge preparations. I_{Kr} block prolonged APD in control preparations as expected. However, they found that I_{Kr} block in HF cells caused less prolongation of the ventricular APD compared to non-failing cells, suggesting the possibility of reduced functional I_{Kr} in HF myocytes (223). No differences have been observed in mRNA expression of Kv11.1 (*KCNH2*) or Kv7.1 (*KCNQ1*) between HF or control patients (249, 545). However, the mRNA expression of KCNE1, which modifies I_{Ks} by slowing activation/deactivation kinetics and positively shifting the voltage-dependence of activation, was found to be increased in HF patients in several studies (67, 545). In HF, reductions in I_{Ks} or I_{Kr} will delay repolarization, leading to ventricular APD prolongation and thus, contribute to a higher EAD propensity.

Inward Rectifying Channels—Decreased density of I_{K1} has been reported in multiple studies involving ventricular myocytes from human HF patients, tachypaced HF-induced dogs, tachypaced HF-induced rabbits, and pressure/volume overload HF-induced rabbits (56, 250, 287, 288, 388, 413). Reductions in I_{K1} may contribute to reduced repolarization reserve, ventricular APD prolongation, and may increase risk for DAD-induced ventricular arrhythmias (363, 388, 444). Conversely, two reports in tachypaced HF-induced rabbits found no changes in I_{K1} (413, 492). Although the majority of studies find a reduction of I_{K1} in HF ventricular myocytes, the molecular mechanism for I_{K1} downregulation in HF is not understood. Kir2.1 mRNA expression appears to be unchanged in human HF, suggesting post-translational modification reduces I_{K1} (249, 543).

Ca^{2+} Handling Proteins—HF causes significant changes in the function and regulation of Ca^{2+} handling proteins such as NCX, RyR, and SERCA2a. Most studies suggest that NCX function, mRNA expression, and protein expression is increased in isolated ventricular myocytes from human HF patients, tachypaced HF-induced dogs, and pressure/volume overload HF-induced rabbits (53, 365, 386, 404, 465). However, one study involving human left ventricular myocytes reported no change in NCX function (383). Similar studies commonly revealed that Ca^{2+}-reuptake into the SR by SERCA2a is decreased along with mRNA and protein expression in HF (53, 261, 365, 386, 439, 458, 465). SERCA is regulated by PLB. When PLB is dephosphorylated, it reduces SERCA function by decreasing SERCA's affinity for Ca^{2+}. β-adrenergic stimulation typically triggers PKA phosphorylation of PLB, thus increasing SERCA reuptake of Ca^{2+} into the SR (174). In HF, PLB expression is not altered, but phosphorylation of PLB is decreased, which contributes to the reduced function of SERCA (231, 441).

Although, NCX is a reversible transporter, it normally extrudes one Ca^{2+} ion for three Na^+ ions generating a net depolarizing current, I_{NCX}. Since SERCA function is reduced in HF, the myocyte has a higher requirement for NCX to remove Ca^{2+} from the cytosol and increased activity of I_{NCX} could lead to ventricular APD prolongation (24, 219, 220). Alternatively, in HF diastolic $[Na^+]_i$ is elevated and Ca^{2+}-transients are dampened; therefore, reverse NCX function (Ca^{2+} influx) may be favored (549).

Lastly, SR Ca^{2+} leak is enhanced at any given SR Ca^{2+} load and is linked to an increase open probability of the RyR in human HF, tachypaced HF-induced dogs, and pressure/volume overload HF-induced rabbits (52, 447). It was originally shown that PKA phosphorylation of RyR2 increases the open probability of RyR2 by favoring disassociation of RyR2 with FKBP12.6 (an RyR inhibitory protein) (322). In HF, RyR2 was found to be hyperphosphorylated, explaining the increase SR Ca^{2+} leak via RyR2. Several groups have since been unable to recapitulate these results and the role of PKA hyperphosphorylation in HF remains controversial today (48, 51, 127, 163, 182, 184, 294, 463, 505, 564). However, there is more concise evidence that CaMKII phosphorylation of RyR2 is increased in human and rabbit HF and inhibition of CaMKII reduces SR Ca^{2+} leak (2, 126, 129, 130, 259). Oxidation by reactive oxygen species (ROS) can also activate RyR2 and CaMKII; therefore, in HF where ROS is elevated, a synergistic activation of RyR2 contributes to further SR Ca^{2+} leak (162, 397, 445, 480).

In all, the combination of 1) increased NCX function, 2) decreased SERCA function and SR Ca^{2+} reuptake, and 3) increased open probability of RyR and SR Ca^{2+} leak create significant cellular dysfunction in HF. These will lead to a decreased SR Ca^{2+} load, dampened Ca^{2+} transients, decreased contractility, and increased cytosolic Ca^{2+}. The Ca^{2+} instabilities present in HF increase risk for DADs, ventricular arrhythmias, and ultimately, ventricular fibrillation.

In general, HF leads to severe impairment in electrophysiological function due to remodeling of several ion channels and regulatory proteins as discussed. It is likely that significant synergism exists among these mechanisms and that arrhythmias arise via the interplay of multiple aspects of HF-induced remodeling. Indeed, a recent study from our

group found that pharmacological inhibition of I_{K1} or an increase in RyR sensitivity that facilitates SR Ca^{2+} release were insufficient separately to promote arrhythmia in intact normal rabbit hearts following local sympathetic stimulation. However, pharmacologically inducing both of these HF-like phenotypes simultaneously led to a significantly increased propensity to focal ventricular tachycardia lasting several minutes following a single induction (Figure 9) (343). These findings suggest that multiple factors likely conspire to the increased arrhythmic risk in HF, such that a multi-targeted approach might provide optimal anti-arrhythmic treatment.

Role of the Autonomic Nervous System in Ventricular Arrhythmia

In addition to ionic remodeling, cardiac pathology (including HF and myocardial infarction) often leads to significant remodeling of the structure and function of the cardiac autonomic nerves. Remodeling of sympathetic neurotransmission is particularly arrhythmogenic and is paradoxically associated with both hyper- and hypo-innervation and as well as altered neurotransmitter release. Regional hyper-innervation was one of the first types of nerve remodeling to be linked to arrhythmia in humans (96) and has now been well documented in many species and various cardiac pathologies (reviewed in (105)). Indeed, our group recently demonstrated the mechanistic basis by which localized sympathetic stimulation leads to the generation of ectopic beats (344). Recently, however, three clinical studies have revealed that the degree of sympathetic hypo-innervation (quantified with nuclear imaging) is a significant predictor of ventricular arrhythmia risk (66, 358), predicting cardiac arrest independent of infarct size and ejection fraction (165). Thus, it seems as if the explanation for these contradictory findings lies in heterogeneity of sympathetic transmission. Indeed, Rubart and Zipes have postulated that heterogeneous remodeling of the sympathetic nerves leads to differential remodeling of myocardial electrophysiological properties (as discussed above) and an increased risk for ventricular arrhythmia (415). In addition, there is now evidence of cholinergic transdifferentiation of the cardiac sympathetic nerves in HF, meaning that instead of producing and releasing norepinephrine, the cardiac sympathetic nerves undergo a phenotypic switch to produce the parasympathetic neurotransmitter, acetylcholine (252). The electrophysiological consequences of this transdifferentiation have yet to be determined, but these provocative findings add yet another layer to the complex regulation of ion channels in HF.

Conclusion

Regionally diverse electrophysiological properties and function are inherently due to the heterogeneity of ion channel expression throughout the heart. Understanding this diversity and the ionic basis of electrophysiological activity is fundamentally important for the investigation of arrhythmia mechanisms and responses to ion-channel blocking drugs. In heart disease, it is important to elucidate how ionic remodeling alters the regional specificity of ion channel expression and function. To accomplish these goals in the future, an improved understanding of the mechanisms underlying normal and abnormal activity of the human heart will require comparative studies of cardiac gene/protein expression and modification, electrophysiology, and excitation—contraction coupling throughout various regions of the heart, both in healthy and pathophysiological situations. Subsequent studies that relate human *vs*. animal heterogeneity and disease-induced remodeling, along with in

silico-based strategies will be useful approaches for translating information from animal to human disease. Additional development and validation of integrative multi-scale computational models of the human (or species-specific) heart in health and disease that incorporates regional heterogeneity, as well as ionic, structural, contractile, neurohormonal maladaptive responses across scales is needed. These experiments and models will be useful to mechanistically link subcellular and cellular abnormalities to potentially patient-specific clinical phenotypes, and guide the selection of appropriate anti-arrhythmic treatment.

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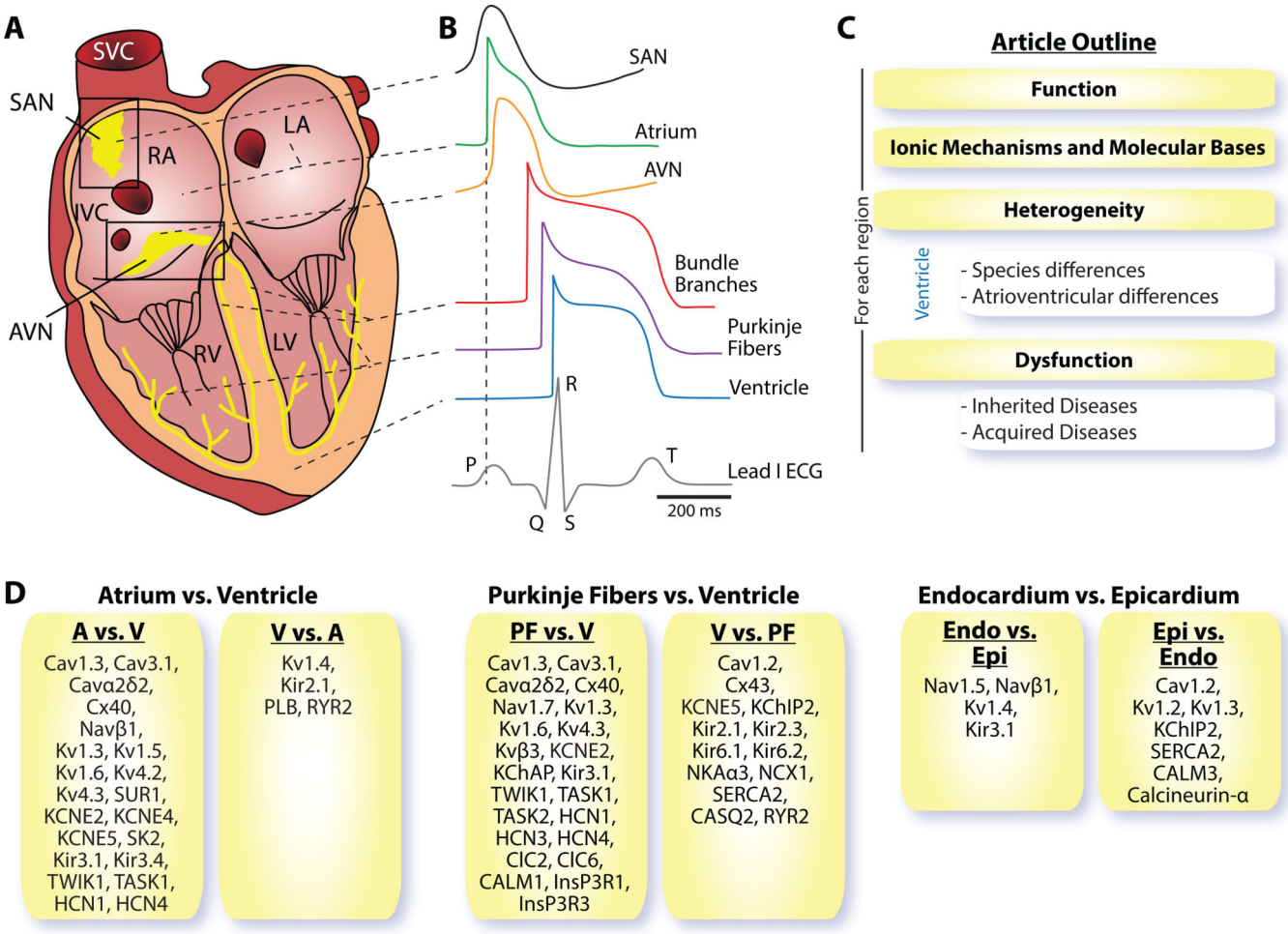

Figure 1. Regional heterogeneity of the electrical properties of the heart

A) Schematic of different regions of the human heart and the corresponding **B)** AP waveforms (below is a representative lead I ECG). **C)** Overview of review organization. **D)** Ion channel and regulatory protein gene expression are compared between corresponding regions of the heart (modified from (178) with permission). SVC: superior vena cava, SAN: sinoatrial node, RA: right atrium, LA: left atrium, IVC: interventricular septum, AVN: atrioventricular node, RV: right ventricle, LV: left ventricle

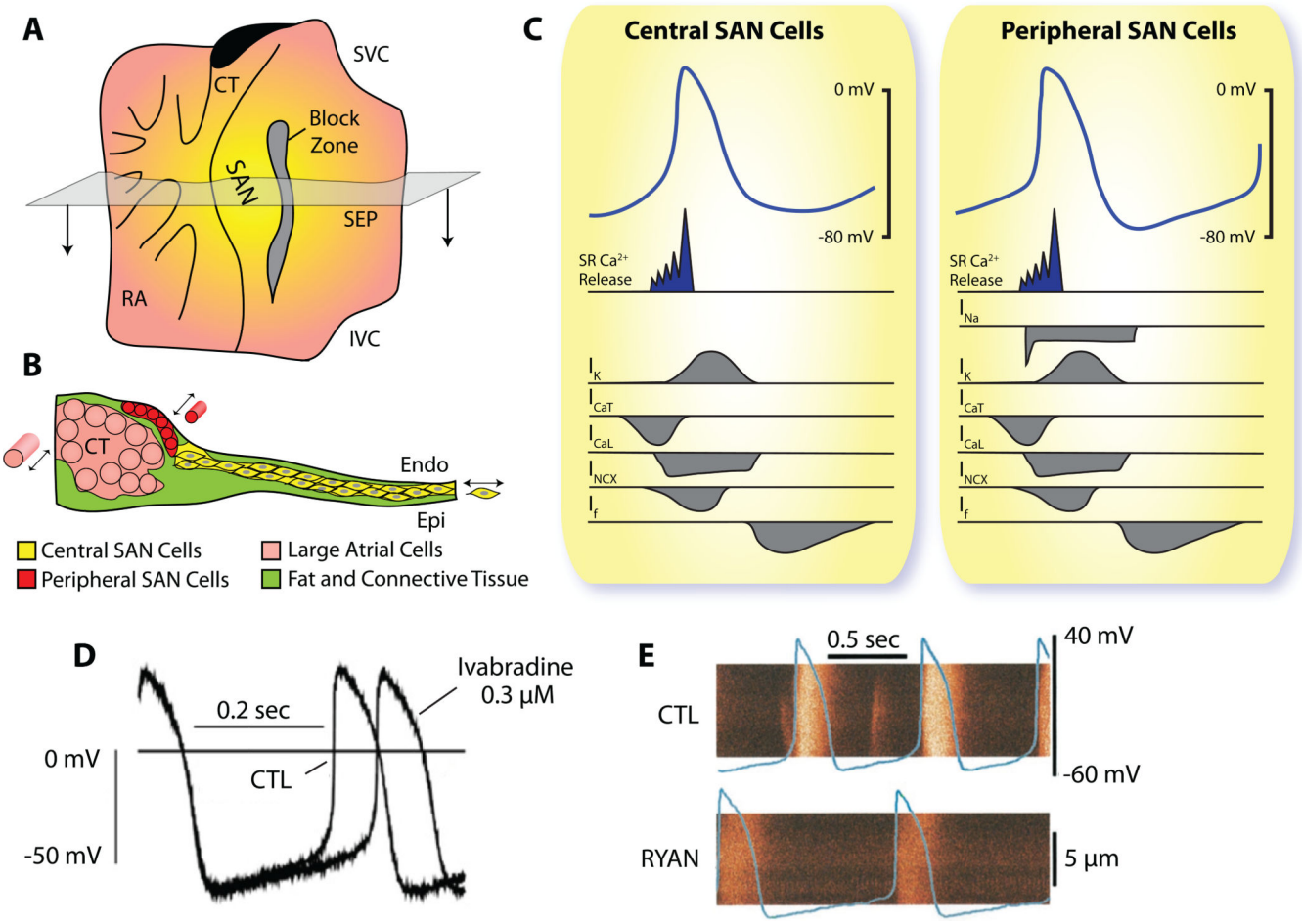

Figure 2. SAN structure and function

A) Schematic showing endocardial view of SAN area (location corresponds to box around SAN in Figure 1A). Approximate area of functional conduction block is shown in gray. **B)** Transmural view of SAN showing organization of central and peripherial SAN cells. Redrawn from (74) with permission. **C)** Example APs and ionic currents from central and peripheral SAN cells. Redrawn from (375) with permission. **D)** Ivabradine, an I_f blocker, slows SAN beat rate via slowing the rate of diastolic depolarization (with permission from (85)). **E)** Slowing of SAN beat rate also occurs with ryanodine, a blocker of RyR Ca^{2+} release, demonstrating the importance of the Ca^{2+} clock in contributing to normal SAN pacemaking (with permission from (64)). CT: crista terminalis, CTL: control, Endo: endocardium, Epi: epicardium, IVC: inferior vena cava, RA: right atrium, RYAN: ryanodine, SEP: inter-atrial septum, SVC: superior vena cava

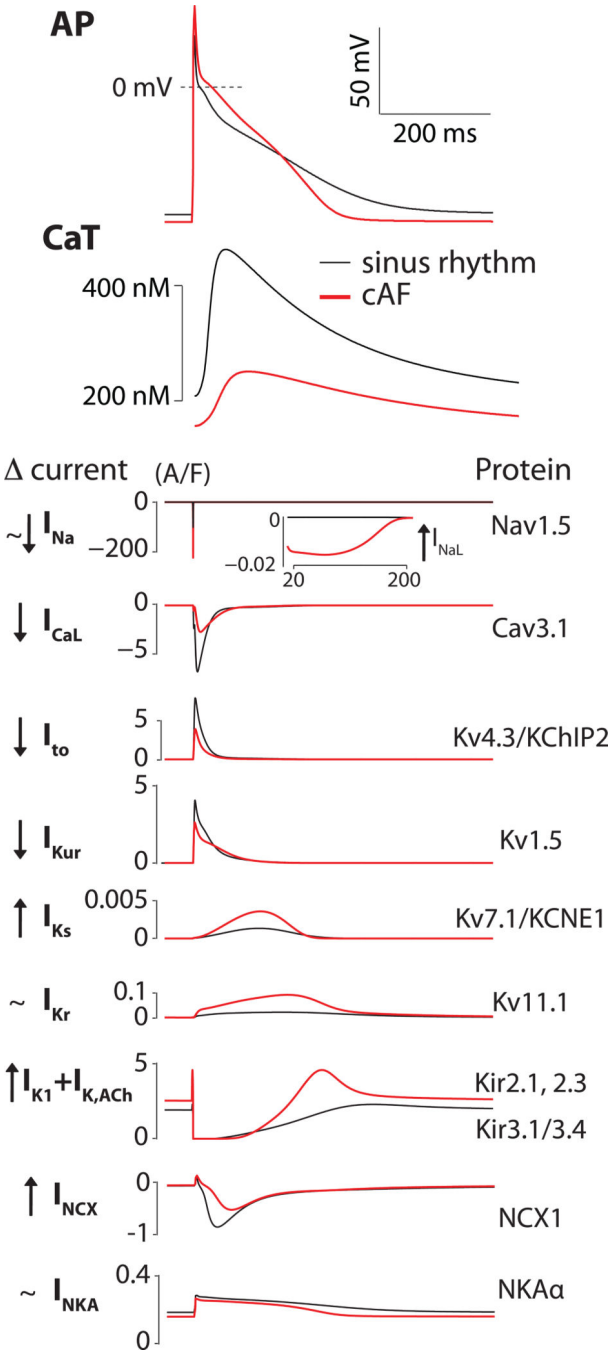

Figure 3. Atrial myocyte function and dysfunction

AP, CaT, and major underlying ionic currents simulated with computational models of human atrial sinus rhythm (black) and AF (red) myocytes. Modified from (196).

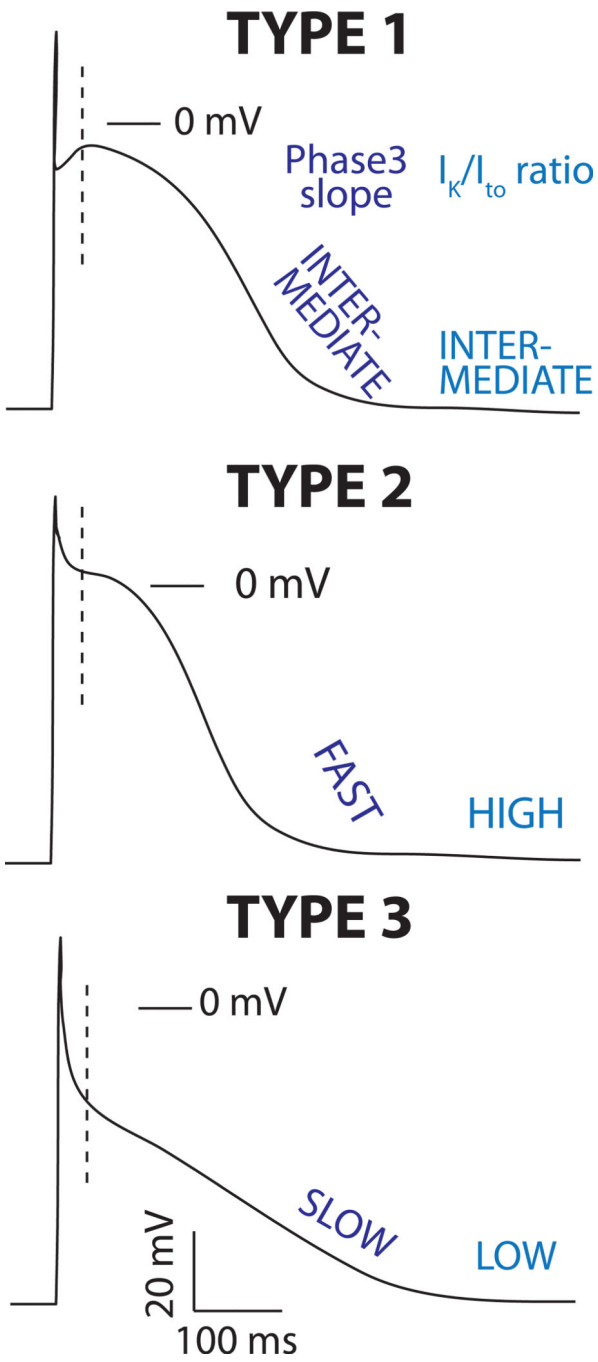

Figure 4. Heterogeneity of atrial electrophysiology

Three different outward current patterns in human atrial myocytes confer distinct AP shape and properties (redrawn from (541) with permission).

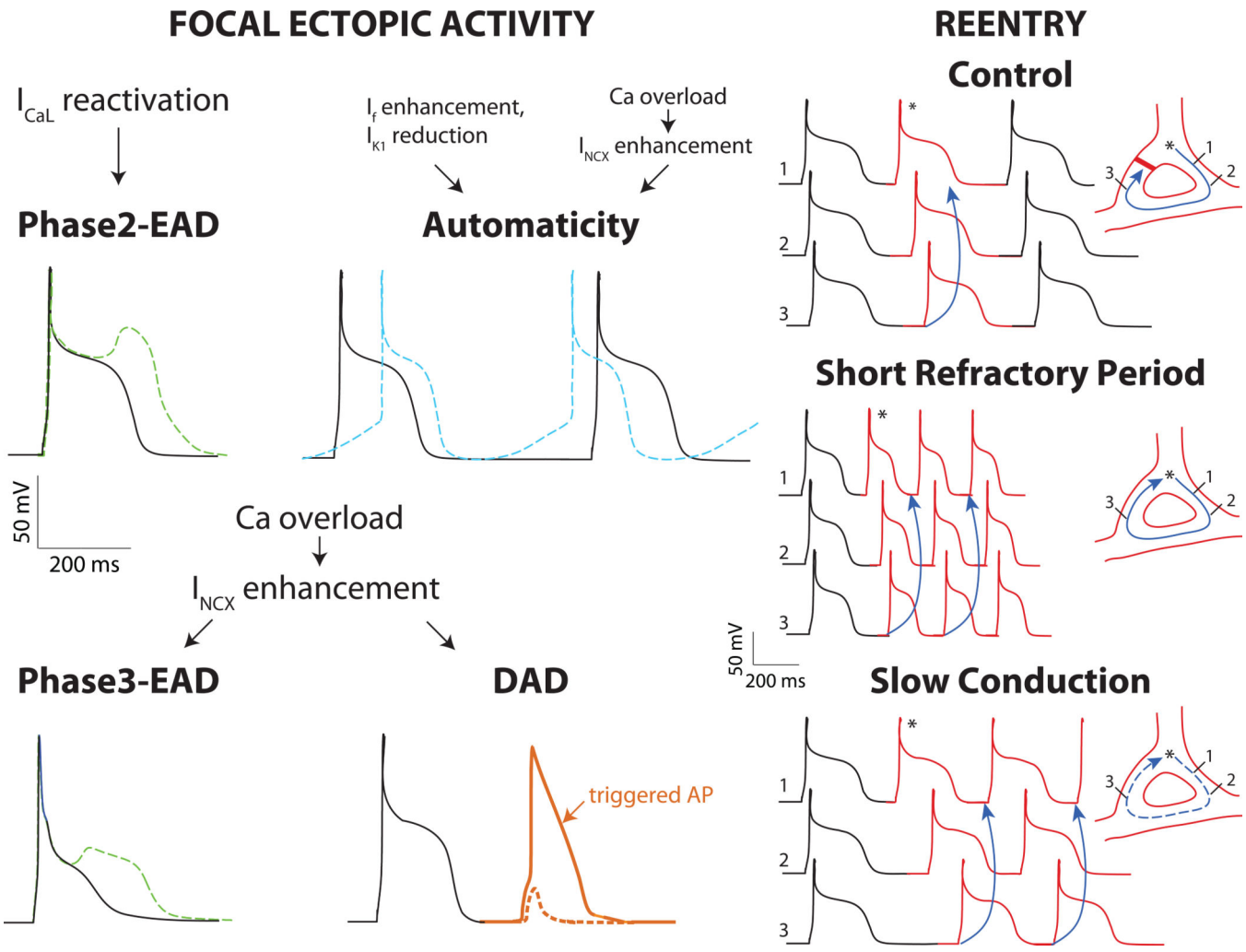

Figure 5. Ionic mechanisms of ectopic activity and reentry

Left: cellular mechanisms of early- and delayed afterdepolarizations and cardiac cell automaticity. Right: mechanisms of reentry, redrawn with permission from (531).

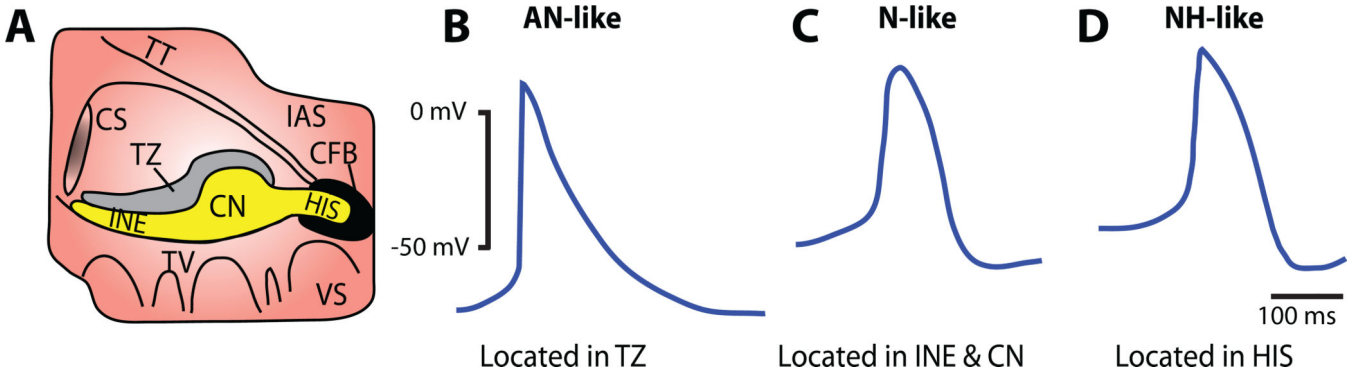

Figure 6. AVN structure and function

A) Schematic showing endocardial view of AVN area (location corresponds to box around AVN in Figure 1A). Redrawn from (232) with permission. **B)** Example AN-like AP. **C)** Example N-like AP. **D)** Example NH-like AP. Panels B-D redrawn with permission from (342). AN: atrio-nodal, CFB: central fibrous body, CN: compact node, CS: coronary sinus, HIS: penetrating His bundle, IAS: inter-atrial septum, INE: inferior nodal extension, N: nodal, NH: nodal-His, TT: tendon of Todaro, TV: tricuspid valve, TZ: transitional zone, VS: ventricular septum

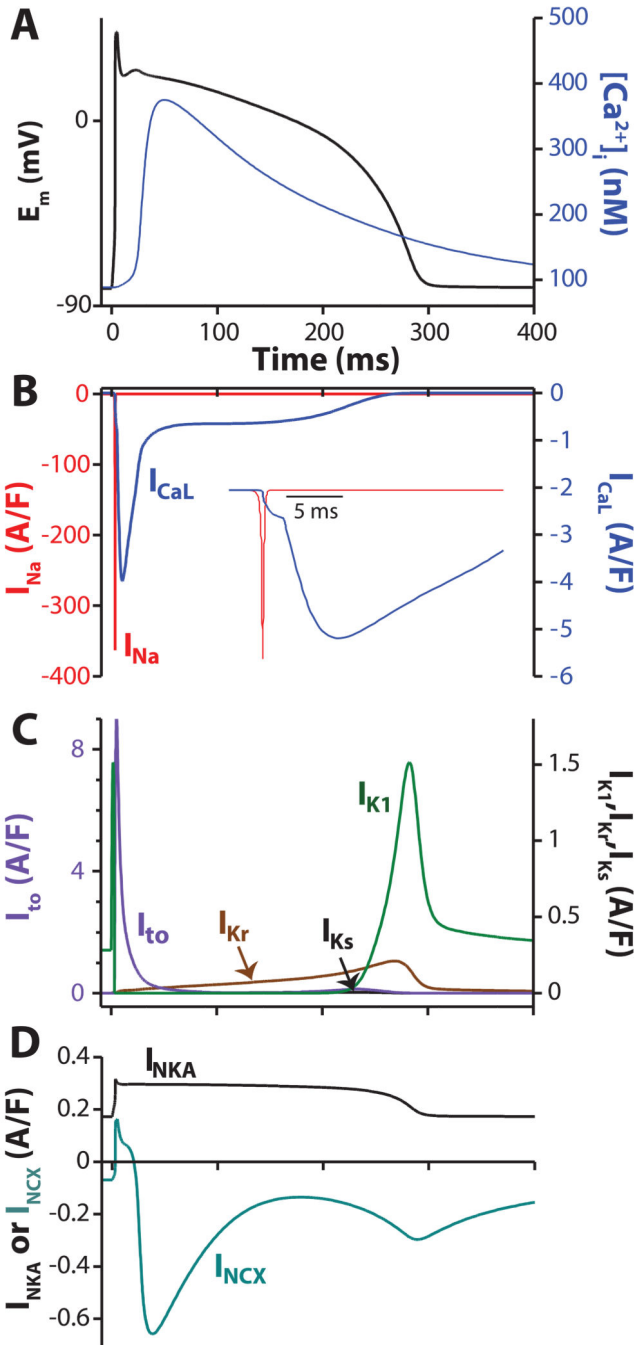

Figure 7. Ventricular AP and ion currents

Depicted in this figure areh **A)** simulated human ventricular AP (black) and CaT (blue). **B)** The major depolarizing Na^+ (I_{Na}, red) and Ca^{2+} (I_{CaL}, blue) currents (inset shows the different time-course of activation and current decay), **C)** the major repolarizing K^+ currents (I_{to}, purple; I_{Kr}, brown; I_{Ks}, black, and I_{K1}, green), and **D)** Na^+/Ca^{2+} exchange (I_{NCX}, turquoise) and Na^+/K^+ pump (I_{NKA}, black) currents during a ventricular AP are shown (194). Redrawn with permission from (192).

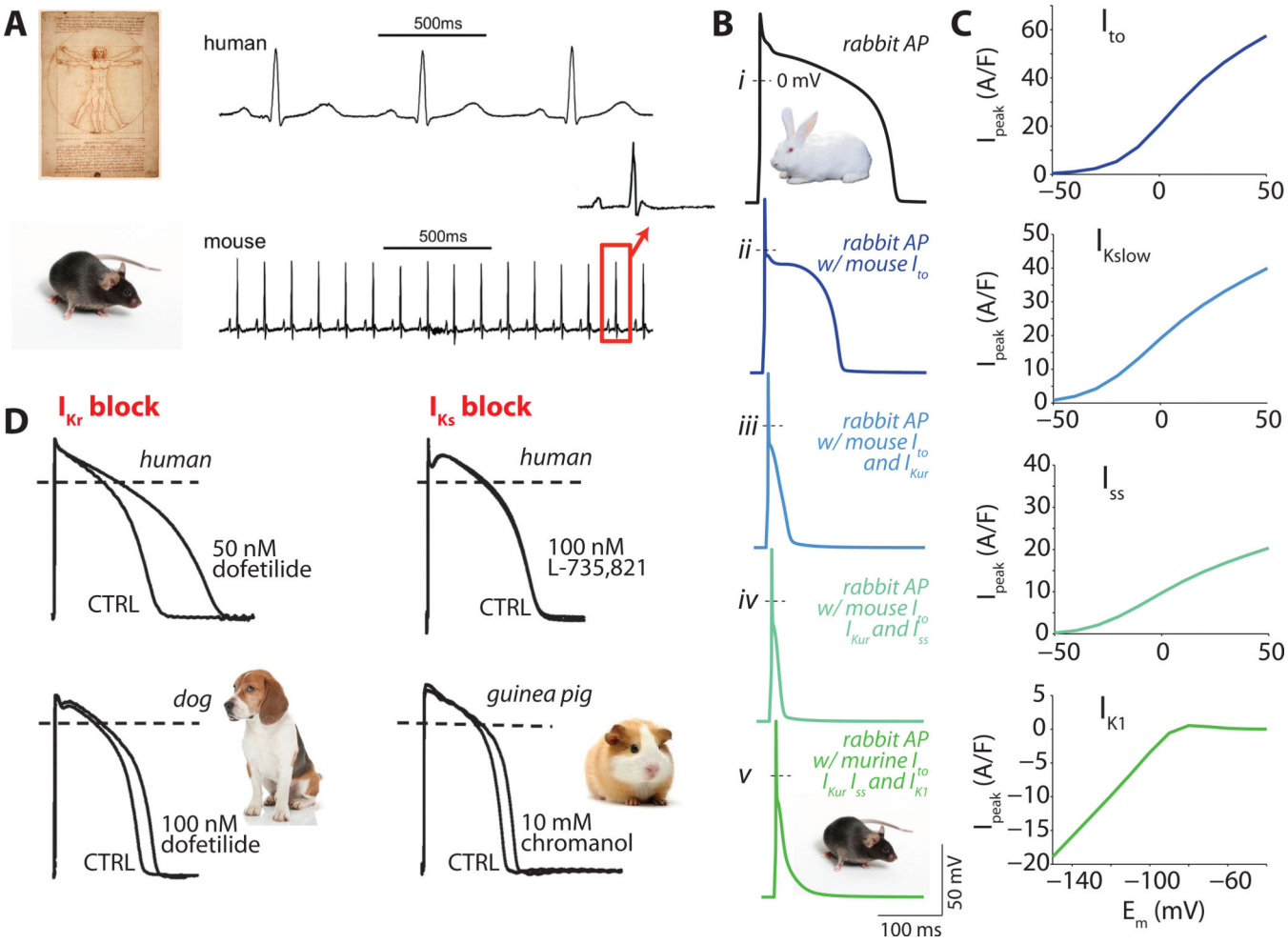

Figure 8. Species Differences in ventricular AP waveforms and drug response

A) Representative traces of ECG recordings from lead I of a human and mouse are depicted (redrawn from (251)). Inset shows a single P-S interval of the mouse ECG. **B)** A rabbit ventricular AP (*i*) is shortened and loses its plateau (*ii–v*) as mouse K^+-currents are integrated. **C)** The simulated I–V relations of mouse I_{to}, $I_{k,slow}$, I_{ss}, and I_{K1} that are added to the rabbit AP simulation are plotted (reprinted from (339)). **D)** Shown are ventricular AP recordings of I_{Kr} or I_{Ks} block in human, dog, or guinea pig. The figure demonstrates the species-specific sensitivity to drug block and changes in AP morphology (reprinted with permission from (416)).

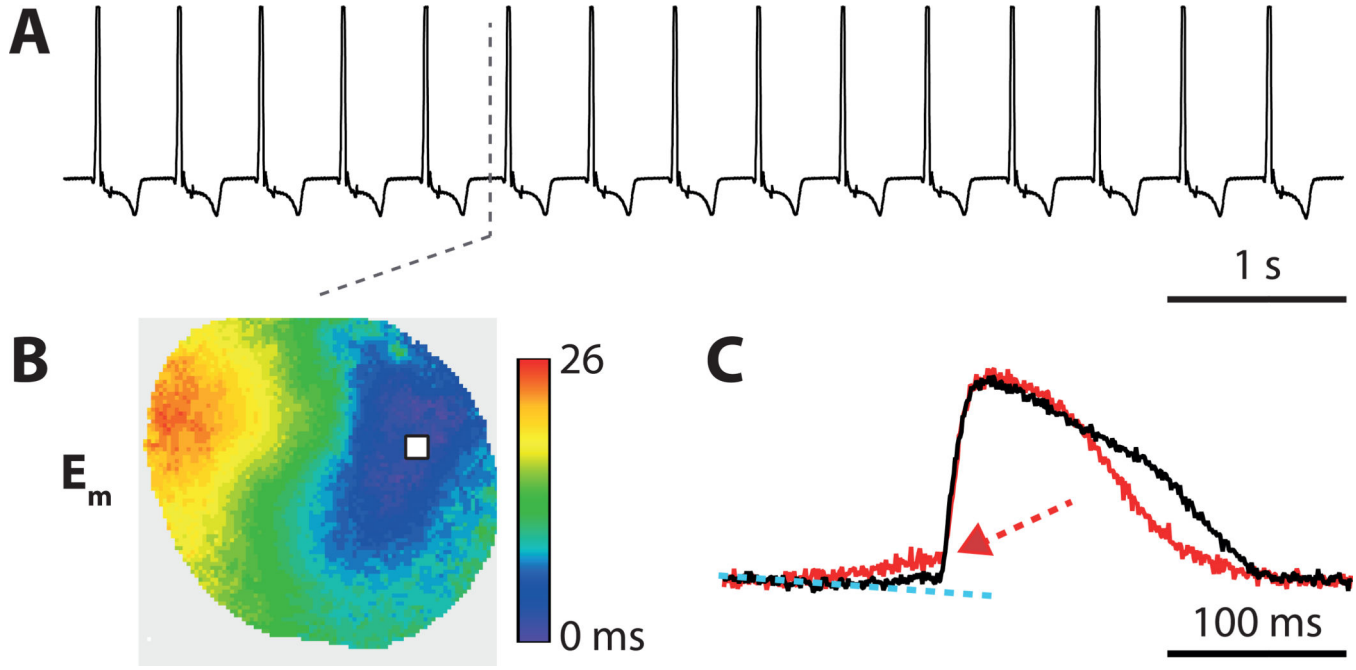

Figure 9. Multiple mechanisms underlie ventricular arrhythmia in HF

A) Sustained focal ventricular tachycardia (VT) induced following local sympathetic stimulation in a normal rabbit heart pretreated with 50 μM $BaCl_2$ to reduce I_{K1} and 200 μM caffeine to sensitize RyR. When applied simultaneously, a highly arrhythmogenic phenotype was observed, but neither condition alone ($BaCl_2$ or caffeine) produced an increase in arrhythmic events (not shown). **B)** Activation map demonstrating the focal origin and spread of propagation of a single beat of VT. **C)** Superimposed E_m (black) and $[Ca^{2+}]_i$ (red) traces from the origin of focal activity showing diastolic E_m and $[Ca^{2+}]_i$ elevation (reprinted from (343)).

Table 1

Molecular bases of altered EC Coupling in human AF (changes *vs.* sinus rhythm) [Modified from (193)].

Cell Size/Structure	
Size	Increased length and width (350)
C_m	Increased (94)
Sarcolemmal Ion Currents	
I_{Na}	No changes (69, 82) Steady-state inactivation shifted right (69) Slightly reduced current density (459) Late current increased (459)
I_{CaL}	Reduced current density by ~50% (112, 148, 509, 521, 560) No changes in voltage dependence of activation and inactivation (509)
I_f	Increased mRNA levels (274)
I_{to}	Reduced density −80% in the RA −45% in the LA (69, 79, 94, 148, 191, 510, 560)
I_{Kur}	Reduced density −55% in the RA −45% in the LA (79, 94, 113, 148, 510) Unchanged (69, 191, 560)
I_{Ks}	Increased 2-fold (94)
I_{K1}	Upregulated +100% (69, 146, 148, 510, 560)
$I_{K,ACh}$	Increased basal current by receptor-independent, constitutively active component; increased (69) or reduced carbachol-activated current (145, 146, 523)
I_{SK}	Increased expression (398) or membrane trafficking (373).
I_{KATP}	Decreased (28) Increased (561)
Ca and Na handling	
I_{NCX}	Upregulated (160, 350, 429, 521)
SERCA	Reduced maximal pump rate (521) and protein expression (160)
PLN	Enhanced PKA and CaMKII phosphorylation (160) Unaltered CaMKII-dependent phosphorylation (350)
RyR	Increased phosphorylation at PKA and CaMKII sites (350, 518, 521) resulting in increased channel open probability (522) and SR Ca^{2+} leak (228, 350)
I_{NKA}	Unchanged function (559)
Ankyrin-B	Downregulated (125)
Protein kinases and phosphatases	
CaMKII	Increased expression (481) and phosphorylation (350)
PKA	Similar activity in cAF *vs.* sinus rhythm (160)
PP1, PP2A	Higher activity (160)
Myofilaments	
	Reduced maximum rate of tension generation and maximum active tension, reduced passive tension, and increase in myofilament Ca sensitivity (40) No changes in maximum force and passive force, reduced rate of tension redevelopment (159) Increased phosphorylation of cMyBP-C (40) Decreased phosphorylation of cMyBP-C (160) No changes in cTnI phosphorylation (40, 160)

Table 2

Congenital ventricular arrhythmia syndromes

Disease	Current Affected	Gene (protein)	Frequency	Key Reference
Long QT syndrome (LQTS): Romano Ward syndrome (autosomal dominant)				
LQT1	I_{Ks}, ↓ amplitude	*KCNQ1* (Kv7.1)	~40%	(538)
LQT2	I_{Kr}, ↓ amplitude	*KCNH2* (Kv11.1, hERG)	~40%	(128)
LQT3	I_{NaL}, ↑ late current	*SCN5A* (Nav1.5)	~5–10%	(540)
LQT4 (ankryin-B disease)	I_{NCX}, I_{NaK}	*ANK2* (Ankyrin B)	Rare	(427) (334)
LQT5	I_{Ks}, ↓ amplitude	*KCNE1* (KCNE1, MiNK1)	~5%	(462)
LQT6	I_{Kr}, ↓ amplitude	*KCNE2* (KCNE2, MiRP1)	~3%	(1)
LQT7 (Andersen-Tawil syndrome)	I_{K1}, ↓ amplitude	*KCNJ2* (Kir2.1)	Rare	(489)
LQT8 (Timothy syndrome)	I_{CaL}, ↑ amplitude/ slows inactivation	*CACNA1C* (Cav1.2)	Rare	(461)
LQT9	I_{NaL}, ↑ late current	*CAV3* (caveolin-3)	Rare	(513)
LQT10	I_{NaL}, ↑ late current	*SCN4B* (Navβ4)	Rare	(325)
LQT11	I_{Ks}, ↓ amplitude	*AKAP9* (Yotiao)	Rare	(104)
LQT12	I_{NaL}, ↑ late current	*SNTA1* (α1-syntrophin)	Rare	(498)
LQT13	$I_{K,ACh}$, ↓ amplitude	*KCNJ5* (Kir3.4)	Rare	(576)
LQTS	I_{CaL}, ↑ amplitude/ slows inactivation	*CALM1*, *CALM2* (calmodulin)	Rare	(124)
LQTS: Jervelle & Lange-Nielsen syndrome (associated with deafness, autosomal recessive)				
JLN1	I_{Ks}, ↓ amplitude	*KCNQ1* (Kv7.1)	Rare	(352)
JLN2	I_{Ks}, ↓ amplitude	*KCNE1* (KCNE1, MiNK1)	Rare	(436)
Brugada syndrome (BrS)				
BrS1	I_{Na}, ↓ amplitude	*SCN5A* (Nav1.5)	~20–30%	(107)
BrS2	I_{Na}, ↓ amplitude	*GDP1-L* (glycerol-3-phosphate dehydrogenase)	Rare	(304)
BrS3 (SQT4)	I_{CaL}, ↓ amplitude	*CACNA1C* (Cav1.2)	~3%	(19)
BrS4 (SQT5)	I_{CaL}, ↓ amplitude	*CACNB2b* (Cavβ2b)	~3%	(19)
BrS5	I_{Na}, ↓ amplitude	*SCN1B* (Navβ1)	Rare	(547)
BrS6	I_{to}, ↑ amplitude	*KCNE3* (KCNE3, MiRP2)	Rare	(133)
BrS7	I_{Na}, ↓ amplitude	*SCN3B* (Navβ3)	Rare	(230)
BrS8	I_f	*HCN4 (HCN4)*	Rare	(496)
BrS9	I_{KATP}, ↑ amplitude	*KCNJ8* (Kir6.1)	Rare	(326)
BrS10	I_{CaL}, ↓ amplitude	*CACNA2D1* (Cavα2δ1)	Rare	(90)
BrS11	I_{to}, ↑ amplitude	*KCND3* (Kv4.3)	Rare	(185)
BrS12	I_{to}, ↑ amplitude	*KCNE5* (KCNE5, MiRP4)	Rare	(366)
BrS13	I_{Na}, ↓ amplitude ?	*MOG1* (MOG1)	Rare	(257)
Catecholaminergic polymorphic ventricular tachycardia (CPVT)				

Disease	Current Affected	Gene (protein)	Frequency	Key Reference
CPVT1	↑ SR Ca^{2+} release	*RyR2* (ryanodine receptor)	~60%	(394)
CPVT2	↑ SR Ca^{2+} release	*CASQ2* (calsequestrin-2)	~3–5%	(273)
CPVT3	I_{K1}, ↓ amplitude	*KCNJ2* (Kir2.1)	Rare	(482)
CPVT4	↑ SR Ca^{2+} release	*TRDN* (triadin)	Rare	(412)
CPVT	↑ SR Ca^{2+} release	*CALM1* (calmodulin)	Rare	(364)
Short QT syndrome (SQTS)				
SQT1	I_{Kr}, ↑ amplitude	*KCNH2* (Kv11.1, hERG)	Rare	(81)
SQT2	I_{Ks}, ↑ amplitude	*KCNQ1* (Kv7.1)	Rare	(39)
SQT3	I_{K1}, ↑ amplitude	*KCNJ2* (Kir2.1)	Rare	(395)
SQT6	I_{CaL}, ↓ amplitude	*CACNA2D1* (Cavα2δ1)	Rare	(479)