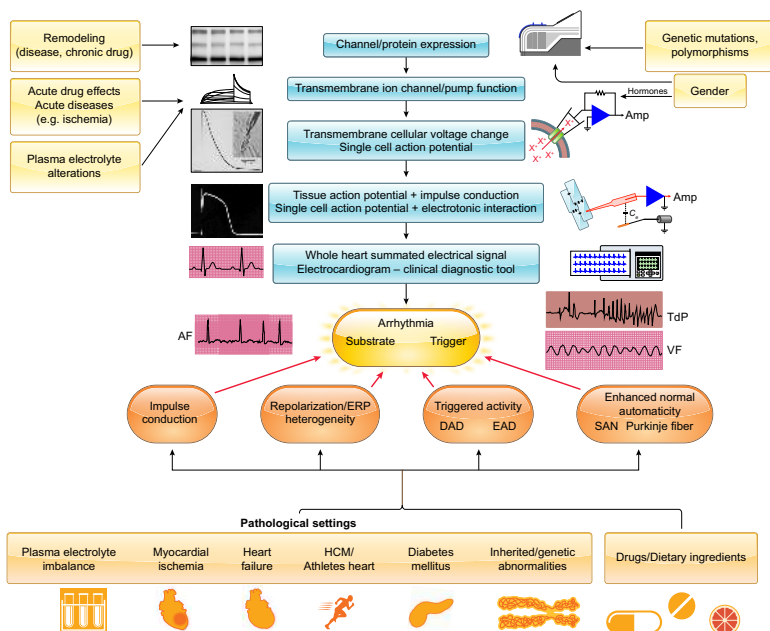


CARDIAC TRANSMEMBRANE ION CHANNELS AND ACTION POTENTIALS: CELLULAR PHYSIOLOGY AND ARRHYTHMOGENIC BEHAVIOR



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KEY WORDS

action potential; arrhythmia; heart; ion channels; remodeling

CLINICAL HIGHLIGHTS

1. Cardiac arrhythmias are major causes of mortality. They most often arise from pathological changes in the electrophysiological properties of myocardial cells. First, this review summarizes the physiology of cardiac action potentials, their regional and species differences, the underlying transmembrane ionic currents, and transporters, with special focus on their human relevance.
2. Progress in computer modeling and vast quantities of experimental data made computerized replication of the action potential, impulse conduction, and simulation of cardiac electrophysiology possible. Current computer models offer improved observability and controllability via utilization of different modeling scales and can assist future individualized anti-arrhythmic therapy as well as drug electrophysiological safety assessment.
3. A number of diseases evoke changes in the configuration of the action potential caused by altered function and/or densities of transmembrane ion channels and transporters, collectively termed electrical remodeling. Initially, these alterations are often compensatory; however, remodeling significantly contributes to increased arrhythmia susceptibility by impairing impulse generation, conduction, and myocardial refractoriness in these clinical settings. Electrical remodeling in atrial fibrillation, heart failure, hypertrophic cardiomyopathy, myocardial infarction, and advanced age are discussed. Better understanding of the cellular basis of cardiac electrophysiology, electrical remodeling, and mechanisms of arrhythmias has important implications for future clinical therapeutic strategies.

CARDIAC TRANSMEMBRANE ION CHANNELS AND ACTION POTENTIALS: CELLULAR PHYSIOLOGY AND ARRHYTHMOGENIC BEHAVIOR

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Abstract

Cardiac arrhythmias are among the leading causes of mortality. They often arise from alterations in the electrophysiological properties of cardiac cells and their underlying ionic mechanisms. It is therefore critical to further unravel the pathophysiology of the ionic basis of human cardiac electrophysiology in health and disease. In the first part of this review, current knowledge on the differences in ion channel expression and properties of the ionic processes that determine the morphology and properties of cardiac action potentials and calcium dynamics from cardiomyocytes in different regions of the heart are described. Then the cellular mechanisms promoting arrhythmias in congenital or acquired conditions of ion channel function (electrical remodeling) are discussed. The focus is on human-relevant findings obtained with clinical, experimental, and computational studies, given that interspecies differences make the extrapolation from animal experiments to human clinical settings difficult. Deepening the understanding of the diverse pathophysiology of human cellular electrophysiology will help in developing novel and effective antiarrhythmic strategies for specific subpopulations and disease conditions.

action potential; arrhythmia; heart; ion channels; remodeling

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1. INTRODUCTION

The heart is a mechanical pump with the vital role of supplying blood to other organs. In humans, it contracts and relaxes in a regular fashion ~60 times per minute. If the regular heartbeat is interrupted for more than a couple of minutes, the lack of oxygen supply causes irreversible damage to vital organs, including the heart itself, potentially causing sudden cardiac death (SCD). Cardiac contractions, the most important function of the heart, are initiated by a bioelectrical signal, the action

potential (AP) (1), via a process called excitation-contraction coupling (2). The action potential originates in the sinus node cells, propagates through the whole heart via an active electrophysiological process called impulse conduction, and can be measured as the electrical potential difference between the intra- and extracellular space. The stimulus spreads through both atria, causing their contraction. The next stage of propagation is the atrioventricular (AV) node, which passes the signal to the ventricles with a slight delay to provide enough time for the atria to contract. From the AV node, the bundle of His conducts the stimulus along the septal wall to the subendocardial Purkinje fibers, which then stimulate the ventricles, allowing their synchronized contraction. The action potential is determined by the opening and closing of various complex transmembrane proteins, which consist of ion channels and transporters, i.e., pumps or exchangers (3–5). Disturbances of action potential generation and/or conduction can lead to changes in the regular heart rhythm called arrhythmias (6, 7). These disturbances can impair contraction to such a degree that thromboembolic stroke of atrial origin or sudden cardiac death may eventually occur. Therefore, understanding the function and regulation of transmembrane ion channels and transporters, as well as their impact on the cardiac action potential, is essential to understand arrhythmia mechanisms and treat life-threatening cardiac arrhythmias. Arrhythmias are usually diagnosed based on the analysis of electrocardiogram (ECG) recordings, which represent the electrical activity of the

heart as measured on the body surface. The ECG is determined by many variables, including the function of transmembrane ion channels and transporters in the different heart cells and the consequent changes in the membrane potential (FIGURE 1).

The P wave corresponds to the activation (depolarization) and early repolarization of the atrial cells. The QRS complex reflects the time course of the depolarization of the ventricles caused mainly by the activation of the fast sodium channels. The PQ segment mainly indicates the impulse conduction from the atria to the ventricles. The PQ segment also contains the HQ interval, which reflects fast propagation due to the function of the fast sodium current (I_{Na}). In addition, cell-to-cell coupling is low in the AV node (8), which makes impulse propagation through the AV node relatively unsafe. The isoelectric ST segment reflects the plateau phase of the ventricular action potentials. In this phase, membrane potential hardly changes at the cellular level because of the fine balance of opening/closing of different ion channels. The configuration of the T wave shows the repolarization time course of the ventricles, and it reflects the balance between the slowly activating repolarizing potassium and chloride currents and the depolarizing steady-state, so-called “window” sodium (9) and “window” calcium (10) and the slowly decaying, often called “late,” sodium (I_{NaLate}) and slowly inactivating calcium currents (11–15). Analysis of the PP intervals yields important information regarding heart rate and its regularity.

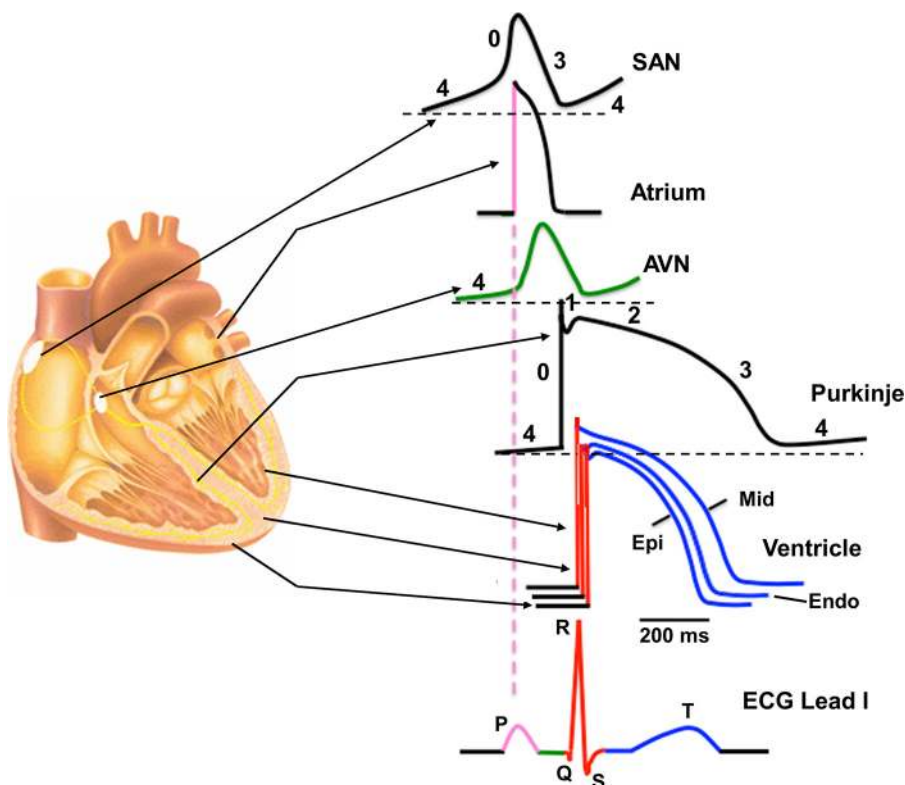


FIGURE 1. Regional differences in cardiac action potential configurations. Schematic cross section of the heart depicting the corresponding action potential configuration from different regions of the heart indicated by arrows. Color-coded sections on the action potentials refer to the corresponding sections on the schematic electrocardiogram (ECG). AVN, atrioventricular node; Endo, endocardial; Epi, epicardial; Mid, midmyocardial; SAN, sinoatrial node.

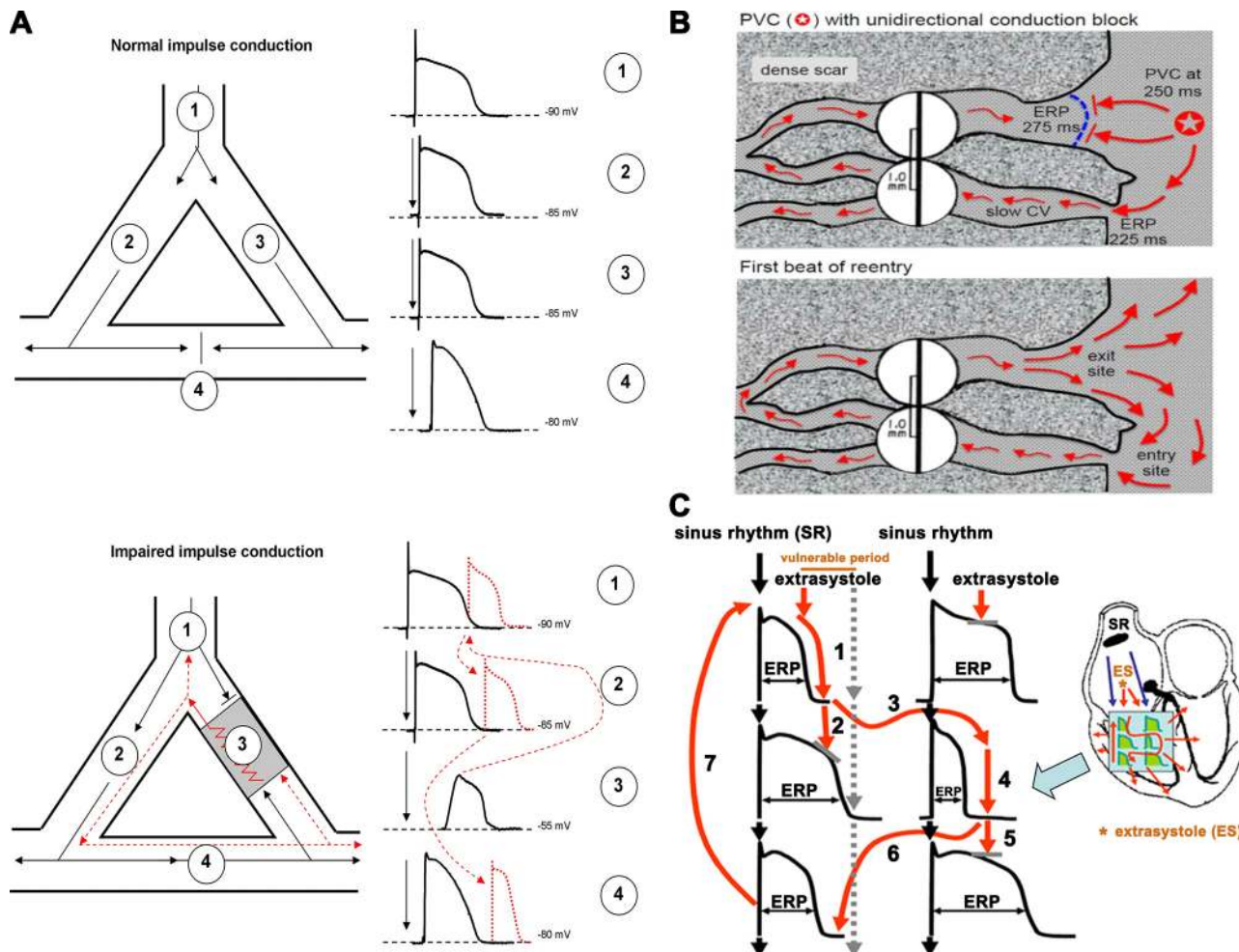


FIGURE 2. *A, top:* an area of branching cardiac tissue, providing separate paths for impulse propagation from proximal (1) to distal (2–4) directions. The separate paths for impulse conduction can be variable, as branching Purkinje fiber-ventricular junctions, ventricular muscle segments with nonconducting fibrosis, scar, or infarcted tissue in the core. If the tissues in these paths are healthy, the impulse conduction is fast and, because of the relatively long effective refractory period (ERP) in cardiac cells, impulses would collide at site 4 and would propagate only into the distal directions. *Bottom:* an area of depolarized myocardium at site 3, due to asymmetric severe local myocardial damage, imposing conduction block from the anterograde direction. However, in the case that the impulse travels from site 4 in the retrograde direction, it can propagate back very slowly into this damaged area, and if its propagation is slow enough to outlast the ERP in front the impulse can reexcite the proximal tissue. Then, this impulse would propagate toward both sites 1 and 2, establishing a circus movement and reentry arrhythmia. *B:* example of a classic mechanism by which a premature ventricular complex (PVC) initiates reentry in the fibrotic border zone of an infarct, due to slow conduction and dispersion of refractoriness. *Top:* a PVC occurring 250 ms after the previous beat arrives too early to propagate through the upper myocyte strand with a long ERP of 275 ms, but it propagates successfully (red arrows) through the lower strand with a shorter ERP of 225 ms (entry site). The impulse propagates slowly (slow CV), eventually reaching the upper strand from the opposite direction. *Bottom:* if the total conduction time is >275 ms, the interface of the upper strand with normal tissue (exit site) has recovered excitability, and the impulse can then propagate through the region of prior conduction block, thus initiating reentry. Dispersion of refractoriness is caused by electrical remodeling. The slow propagation is due to zig-zag conduction through the myocyte strands as well as gap junction remodeling. (Reproduced from Ref. 17 with permission.) *C:* schematic illustration of functional reentry mechanism without a well-defined anatomical obstacle. The arrhythmia substrate is represented by artificially enhanced action potential duration differences. In normal circumstances, impulses originating from the sinus node (black arrows) use physiological pathways to propagate through atrial and ventricular tissue and the conduction system. An early ectopic impulse (trigger, red arrow) can only propagate via pathways where the tissue is not depolarized, and consequently its refractoriness is over, whereas the conduction is blocked in directions where the tissue is not fully repolarized and cells are still in the refractory state. Thus the abnormal impulse can travel in a zig-zag direction through reentry paths created by heterogeneous repolarization and conduction. The dispersion of repolarization creates a time window called the vulnerable period, where extra stimuli could elicit the reentry arrhythmia. However, outside this window extra stimuli would only cause a single or multiple relatively harmless extrasystoles. CV, conduction velocity; ES, extrasystole; SR, sinus rhythm. Reproduced from Ref. 18 with permission.

Cardiac arrhythmia mechanisms are still the subject of intensive research. Because of the large variability in appearances, types (e.g., bradycardia and different types of tachycardia), locations (supraventricular or ventricular), and underlying diseases, it is

widely accepted that there is not a single mechanism to explain how arrhythmias originate. Therefore, patients are often treated with little knowledge regarding the mechanisms and/or causes of the arrhythmia.

The majority of cardiac arrhythmias are the result of an enhanced proarrhythmic substrate combined with a trigger (16). Enhanced heterogeneity of repolarization and impaired impulse conduction represent typical arrhythmia substrates (conditions that are prerequisites for arrhythmia development) for severe tachyarrhythmia. Impairment of impulse conduction can be caused by anatomical (FIGURE 2, A and B) (17) or functional (FIGURE 2C) (18) alterations. The process was described long ago, first in the early twentieth century (19). Impulse conduction critically depends on the density and kinetics of inward transmembrane ionic currents. Depolarization of the resting membrane potential (RMP), for example, reduces sodium and calcium inward currents and strongly influences their kinetic properties. This can thus slow impulse conduction and cause unidirectional or bidirectional conduction block, and potentially reentry, underpinning a wide range of cardiac arrhythmias.

As mentioned above, reentrant arrhythmias can be caused by functional causes too, without an anatomically well-defined myocardial damage (FIGURE 2C). This form of reentry is more complex and could involve both impulse conduction and repolarization heterogeneities (arrhythmia substrate) as well as enhanced normal or abnormal automaticity (trigger).

Reentrant arrhythmias are often initiated by an extrasystole formed anywhere in the heart, acting as an arrhythmia trigger (20, 21). Both arrhythmia substrate and trigger, like an extrasystole [premature ventricular complex (PVC)], can be promoted by pathological cardiac conditions (FIGURE 2), e.g., myocardial ischemia, heart failure (7), and genetic diseases (22), or by adverse drug reactions (23). General arrhythmia mechanisms include various cellular aspects, e.g., transmembrane ionic currents, transporters, action potential properties, and automaticity, which are the subjects of this review. However, arrhythmia mechanisms at the whole heart level are more complex, since they are also determined by anatomical and structural properties, impulse conduction, and intercellular communication between myocardial and nonmyocardial cells, like fibroblasts. These factors are beyond the scope of the present work, and the interested reader is referred to other reviews (22, 24–34).

2. CARDIAC ACTION POTENTIAL

The cardiac action potential is a transmembrane potential change, with an amplitude ranging between 60 and 120 mV. It starts from a negative value, i.e., the resting membrane potential (RMP) in working myocardial cells or maximal diastolic potential in spontaneously beating cells (1), ranging from -95 to -40 mV. As in other excitable cells, the RMP is mainly defined by the conductance

of inwardly rectifying K^+ currents and can be roughly estimated by the Nernst equation from the uneven distribution of mainly K^+ ions across the cell membrane. The electrogenic ATP-dependent Na^+-K^+ pump also contributes to the RMP, by exporting 3 Na^+ and importing 2 K^+ (35–38). In healthy conditions, the duration of the action potential (APD) determines the effective refractory period (ERP), defined as the shortest time interval needed before a new stimulus, or an early extrasystole, can elicit another action potential. The relationship between APD and ERP can be disrupted in pathological conditions, for example, in hyperkalemia, resulting in postrepolarization refractoriness (39).

In the context of the cardiac action potential, two aspects should be emphasized. First, there is no such uniform entity as “the cardiac action potential,” since its shape, i.e., the time course of the transmembrane potential changes, differs in the various regions of the heart (FIGURE 1), and therefore different action potentials should be considered and discussed separately. Second, there are significant interspecies differences (40), even when action potentials are recorded from similar regions of the heart. This is an important, and often overlooked, issue, since many experimental results have been obtained in small rodents, recently particularly in transgenic mice.

In general, the cardiac action potential is divided into five distinct phases (FIGURE 1). Phase 0 is the fast depolarization due to an abrupt increase in sodium influx, and it is characterized by the upstroke velocity and can result in an overshoot, i.e., the rapid change of potential from the negative RMP to positive voltage values, reaching a peak of up to $+30$ to $+40$ mV. The overshoot is followed by a return to negative values, in a process called repolarization, which includes phases 1, 2, and 3. Phase 1 is characterized by a transient and relatively fast repolarization brought about by a decrease in sodium influx and a transient increase in potassium efflux and chloride influx. Phase 2 consists of a long-lasting plateau, still at depolarized voltage, during which the membrane potential remains almost constant or decreases slowly, caused by a small net transmembrane current carried by simultaneous calcium (and some sodium) influx and potassium efflux. Phase 3 represents the large repolarization toward the diastolic potential, mostly due to increased potassium efflux and decreased calcium and sodium influx. Phase 4 represents the resting membrane potential in diastole in working myocytes and the spontaneous depolarization in pacemaker cells. In cardiac myocytes that do not beat spontaneously the voltage remains stable at the RMP, whereas in cells exhibiting automaticity the potential gradually changes toward the positive values, in a process called spontaneous diastolic depolarization. When the threshold potential is

reached, a new spontaneous action potential is generated, with a certain cycle length.

There are four common methods to record cardiac action potentials:

- 1) Weidmann and Coraboeuf were the first to record cardiac action potentials in dog ventricular muscle (41) and later in dog Purkinje fibers, using the sharp glass capillary-based microelectrode technique (42). The classical cardiac cellular electrophysiological knowledge gained by using this technique was elegantly summarized in an early monograph entitled *Electrophysiology of the Heart* by Hoffman and Cranefield (1), published in 1960, which is still useful today. This technique is still considered one of the best for accurate cardiac action potential recordings and can be used for both single-cell and tissue recordings. Its major advantages include 1) the ability to accurately record very fast voltage changes and 2) because of the very fine tip of the pipette, very little diffusion takes place out of the pipette solution, having negligible effects on the intracellular milieu. However, since this technique has some limitations (e.g., difficulties in maintaining a stable impalement for extended periods of time), other methods have also been developed and used widely.
- 2) In intact hearts, in in vivo animal experiments, or in clinical studies, where the microelectrode technique is difficult to apply, monophasic action potential recording can also be used, with either a suction electrode (43, 44) or a Franz catheter (45). With this technique, recordings can be easily performed from multiple sites simultaneously, and impalements/attachments are not lost because of vigorous contractions, even in in vivo or ex vivo conditions. However, rapid voltage changes or action potential amplitudes and shapes cannot be determined accurately.
- 3) Since the introduction of the patch clamp by Neher and Sakmann (46–48), the whole cell configuration of this technique has been widely used. In the current-clamp mode, it can record action potentials from isolated myocytes. Despite its widespread use, this technique has important limitations that should be emphasized. First, measurements are performed in single isolated myocytes or, occasionally, cell pairs, and it is uncertain how, and to what degree, different ion channels are influenced by individual enzymatic digestion during the isolation procedure (49). Therefore, even if the recordings show single-cell action potentials with a normal shape, the function of the finely regulated ion channels can be drastically altered from their original condition. Also, the cell is dialyzed with the pipette contents, and its intracellular composition will change. When carefully and deliberately applied, however, this point can also be considered an advantage, as it allows control of the intracellular milieu. It should also be emphasized that single isolated myocytes are devoid of electrotonic interactions from neighboring cells. Therefore, the stochastic

opening/closing behavior of ion channels has a more profound effect on membrane potential than in well-coupled tissue preparations (50). In addition, in multicellular preparations part of the ionic currents are utilized to depolarize neighboring cells during impulse propagation, and this can considerably reduce the action potential peak compared with single cells (51). Hence, action potential measurements in single isolated myocytes obtained with the patch-clamp technique should be interpreted with caution and not directly extrapolated to intact tissue.

- 4) The latest approach to recording cardiac action potentials is the optical mapping technique, which uses voltage-sensitive dyes and allows simultaneous recordings from multiple sites (52, 53). This technique is also excellent for dynamic studies and for investigations of arrhythmia mechanisms (54, 55). Disadvantages of this method include the difficulty of calibration to millivolts, phototoxicity, photodegradation, and photon scattering effects (56). Also, the application of excitation-contraction uncoupling compounds, e.g., blebbistatin, is necessary to avoid motion artifacts (57). These compounds may interfere with the experiments, since, e.g., blebbistatin was reported to elicit anomalous electrical activities (58) and prolongation of action potential duration (59), and inhibition of contraction will also decrease metabolic rate at the concentrations needed for motion artifact reduction.

3. TRANSMEMBRANE ION CHANNELS AND TRANSPORTERS IN THE HEART

The cardiac action potential is the voltage change caused by ions flowing through transmembrane ion channels, via their dynamic and simultaneous opening and closing (11, 60). Therefore, before addressing different regional action potential patterns, we describe the various transmembrane ion channels that have been reported to operate in the heart cells.

Transmembrane ionic currents in the heart are usually measured with the patch-clamp technique in enzymatically isolated myocytes. This allows recording and analysis of unitary currents through single ion channels or all channels on the sarcolemma. Before the introduction of the patch clamp, transmembrane current recordings were less accurate, because of the lack of proper voltage control of the preparation, and fast current changes and gating kinetics were impossible to determine accurately (61). Therefore, much of the knowledge gained before the introduction of the patch-clamp technique has had to be reevaluated, and some currents have been renamed. To the interested reader, we recommend an excellent monograph by Denis Noble, *The*

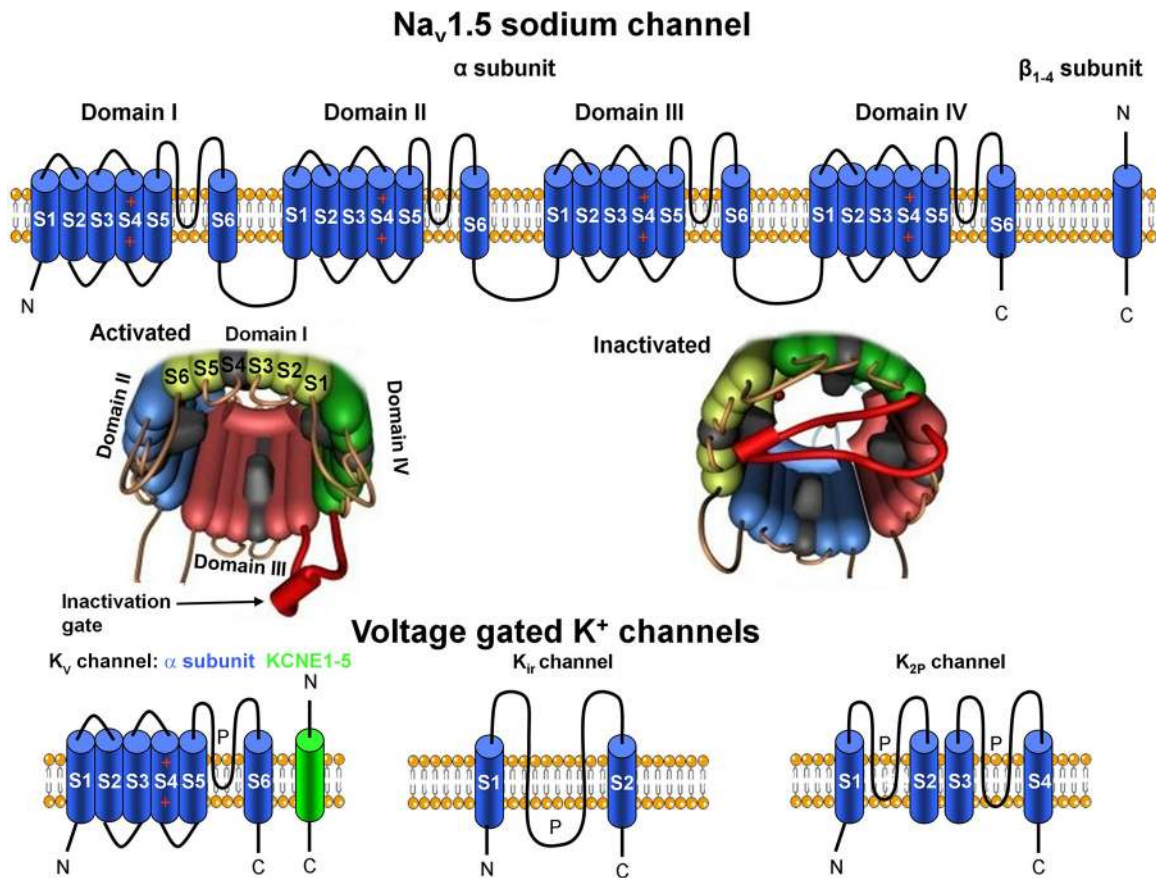


FIGURE 3. Schematic illustration of voltage-gated sodium (Na_v) and potassium (K_v) channels. *Top*: topological models of Na_v1.5 channel subunits and their molecular assembly. Four domains (I–IV) of Na_v α-subunits contribute to individual Na_v channel formation. *Middle*: the activated and inactivated Na_v channel configurations. *Bottom*: the transmembrane topologies of K_v, inward rectifier (K_{ir}), and two-pore domain (K_{2p}) potassium channel subunits.

Initiation of the Heartbeat (62), which deductively and briefly summarizes our knowledge before the use of the patch-clamp technique.

It is important to note that a given ionic current, measured with the patch clamp, does not correspond to a unique ion channel. Certain transmembrane ionic currents can be conducted by several different ionic channels (3, 5), e.g., inward rectifier potassium current (I_{K1}) is carried by inward rectifier potassium (K_{ir})2.1, K_{ir}2.2, K_{ir}2.3, and K_{ir}2.4 channels (5, 63) and tandem of pore domains in a weak inward rectifying potassium channel (TWIK)-related acid-sensitive potassium (TASK) channels (64), whereas transient outward current (I_{to}) is carried by voltage-gated potassium (K_v)4.3, K_v4.2, and K_v1.4 channels. In addition, certain channels like human ether-à-go-go-related gene (hERG) have multiple isoforms (hERG 1a and 1b) (65) with different gating kinetics and drug sensitivities (66). This offers the possibility of pharmacologically modulating specific channel isoforms without interfering with others, and thus avoiding undesirable side effects.

Recent advances in genetics and molecular biology have made it possible to further elucidate the structure of ion channels (FIGURE 3). It is widely known that

most transmembrane ion channels consist of multiple subunits: a pore-forming α and modulatory accessory subunits, which can modify channel gating and serve as possible drug binding or phosphorylation sites (3, 5, 67, 68).

3.1. The Fast Inward Sodium Current

The fast inward sodium current (I_{Na}) is the most important current for impulse conduction in cardiomyocytes, with a diastolic potential more negative than -60 mV (69), and is therefore particularly important in atrial, ventricular, and Purkinje fiber myocytes. This current is responsible for the influx of Na⁺ during phase 0 of the action potential (FIGURE 1 and FIGURE 4), and it is conducted by voltage-gated sodium (Na_v)1.5 channels, encoded by the gene *SCN5A* coassembled with β_{1–4} (*SCN1–4B*)-subunits (70). The high-molecular-weight pore-forming α-subunit contains four repeat domains (labeled I–IV); each domain consists of six transmembrane segments (S1–S6), and the S4 segment is responsible for voltage sensing (FIGURE 3). Special extracellular regions (P loops) between the S5 and S6 segments of the four domains form the structure that is responsible

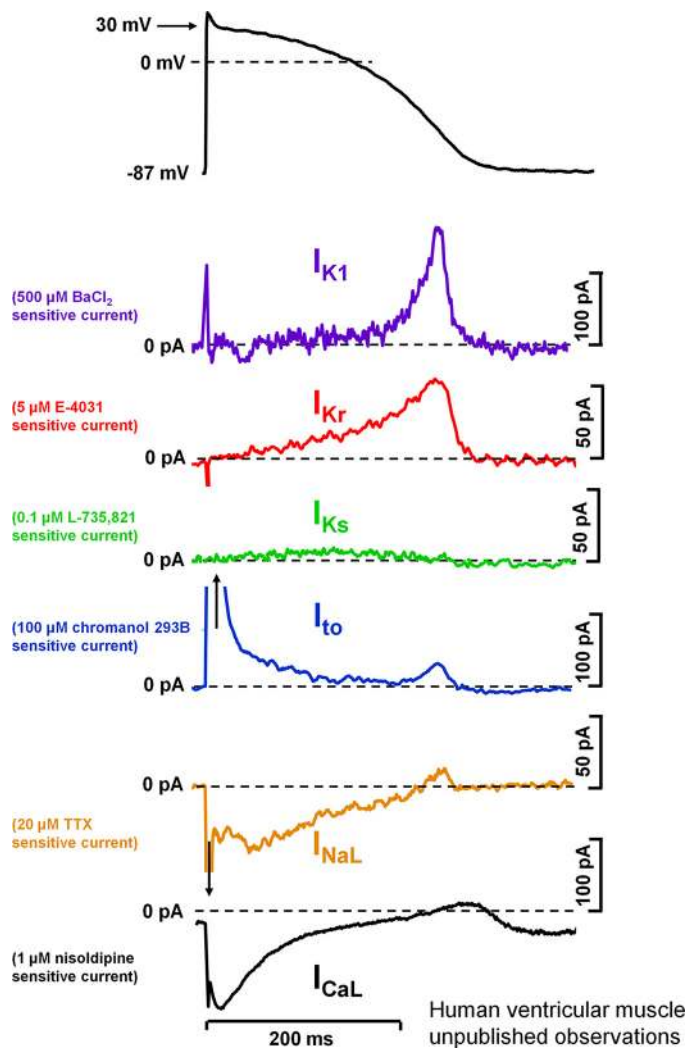


FIGURE 4. Action potential and underlying ionic currents recorded from human ventricular myocytes with the patch-clamp technique applying human ventricular action potential as command pulses at 1 Hz stimulation frequency, in the absence of any sympathetic effects. Inward rectifier potassium current (I_{K1}), rapid (I_{Kr}) and slow (I_{Ks}) components of delayed rectifier potassium current, transient outward current (I_{to}), and L-type calcium current (I_{CaL}) were measured as difference current following application of selective channel inhibitors. I_{NaL} , late sodium current. Unpublished data from our laboratory at the Department of Pharmacology and Pharmacotherapy, University of Szeged.

for the ion selectivity of the channel. The region that links domains III and IV contains the inactivation gate that “plugs” the channel pore after prolonged activation (FIGURE 3). A detailed, comprehensive review on the cardiac sodium channel structure has been published recently (71). $Na_v1.5$ channels open, within a fraction of a millisecond, at potentials more positive than -60 mV, with strong voltage dependence. Since channel density is high, they carry a large inward current, with an amplitude of >100 pA/pF. They also inactivate very rapidly at voltages more positive than -80 mV (at -10 mV with time constant τ_1 of 0.6 ms and τ_2 of 4 ms) (72), with a half-inactivation between -60 and -70 mV. $Na_v1.5$

channels can recover from inactivation with a time constant of 2–20 ms at negative voltages (69, 73, 74). The exact kinetics of their inactivation and recovery are complex and still not fully understood. So far, multiple inactivation kinetics and recovery kinetics from inactivation have been described (12, 69, 75–77).

In addition to this fast component, slow inactivation, occurring over hundreds of milliseconds, has been described (12, 13, 78) and attributed to late openings of $Na_v1.5$ channels (79). Recently, a new term, “late sodium current” (I_{NaLate}), has been used to refer to this current, which, although small in amplitude ($<0.5\%$ of the peak I_{Na}) (79, 80), nonetheless represents an important sustained depolarizing current during phase 2, thus playing a role in maintaining the relatively long plateau of the cardiac action potential (FIGURE 4) (78). This I_{NaLate} is more sensitive to tetrodotoxin (TTX) and other sodium channel inhibitors (81) than the peak I_{Na} (82).

As a steady-state component of I_{Na} , a so-called “window sodium current” in the voltage range from -65 to -15 mV based on a different mechanism than the slow inactivation was also suggested earlier by Attwell et al. (9). This window current was considered to be caused by the overlap between the steady-state activation and inactivation curves. At present, it is still not clear whether such a window current exists, or if the measured overlap is due to an ultraslow inactivation or ultraslow recovery from inactivation when this window current is determined. To better understand the nature of the sodium current during the plateau phase of the action potential, the possible involvement of sodium channels other than the $Na_v1.5$ channel, which is considered to be the major cardiac sodium channel, was also suggested in several studies (83–88). As an example, $Na_v2.1$ α -, β_1 - and β_2 -subunits are highly expressed in human atrial and ventricular cells and Purkinje fibers (84, 85) even if their function has not been explored yet. The expression of various neuronal sodium channel subtypes, e.g., $Na_v1.1$, $Na_v1.2$, $Na_v1.3$, $Na_v1.4$, $Na_v1.6$, and $Na_v1.8$ (encoded by *SCN1A*, *SCN2A*, *SCN3A*, *SCN4A*, and *SCN10A* genes, respectively), has been described in different cardiac preparations (89), but again their functional roles are not fully understood (3, 5, 85, 86, 90). Mishra et al. (86) reported that in failing dog and human hearts neuronal $Na_v1.1$ channels were upregulated and provided significant I_{NaLate} , whereas another recent study (91) showed significant upregulation of $Na_v1.8$ channels in failing human hearts. In addition, selective inhibition of this $Na_v1.8$ current by A-803467 (92) abolished arrhythmogenic Ca^{2+} sparks that were attributed to enhanced intracellular Ca^{2+} load due to increased I_{NaLate} . Mutations in the $Na_v1.8$ encoding gene, *SCN10A*, were reported in patients with atrial fibrillation (AF) (88) and also predisposed to sudden cardiac death (83). Therefore, it is

SCN5A expression in the heart

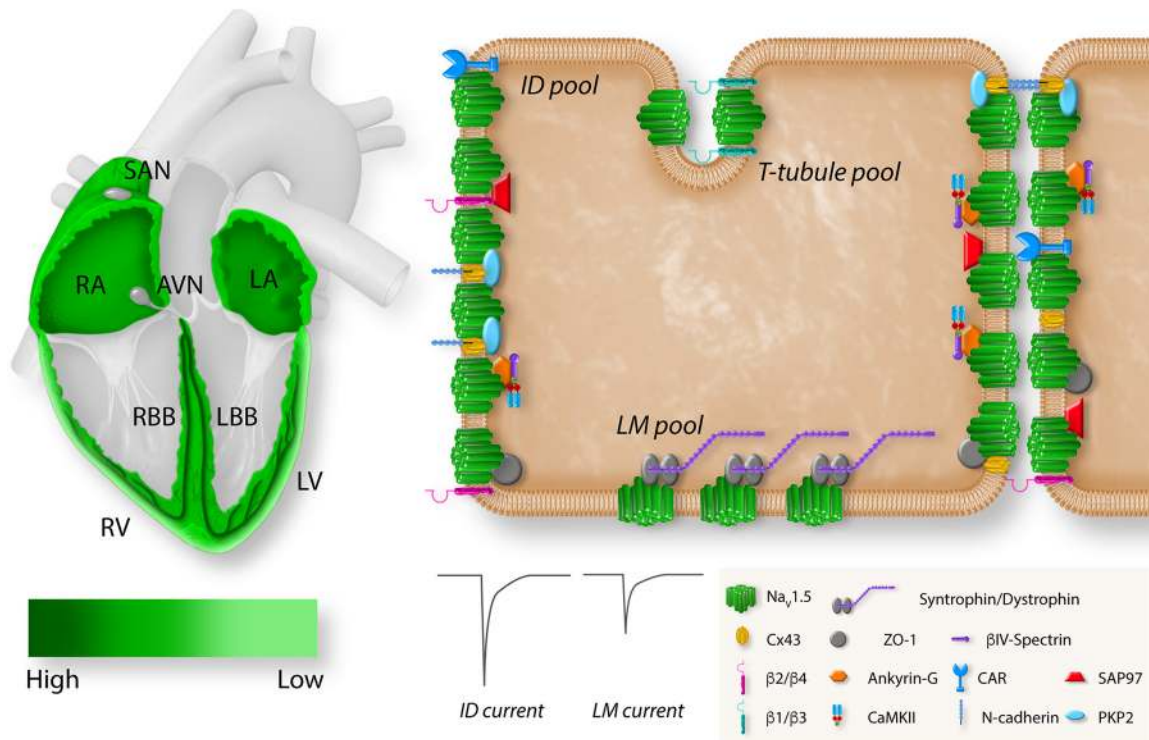
Na_v1.5 localization in the cardiomyocyte

FIGURE 5. Regional and subcellular distribution of *SCN5A*/voltage-gated sodium channel ($\text{Na}_v1.5$) in the heart and cardiomyocytes. *Left:* the expression levels of *SCN5A* in different regions of the heart. Expression of *SCN5A* is highest in the atrioventricular (AV) bundle, His bundle, and right (RBB) and left (LBB) bundle branch (dark green). *SCN5A* is broadly expressed in right (RA) and left (LA) atria and right (RV) and left (LV) ventricle with an epi/endo gradient in the ventricles. *SCN5A* is absent from the central sinoatrial node (SAN) and atrioventricular node (AVN). *Right:* the localization of $\text{Na}_v1.5$ with specific regional partner proteins in the microdomains of a cardiomyocyte: intercalated disk (ID), lateral membrane (LM), and T tubules. The sodium current at the ID is larger than the sodium current at the LM. Reproduced from Ref. 94 with permission.

clear that further studies are needed to elucidate the role of neuronal Na^+ channels in normal and diseased heart (93).

It is known that $\text{Na}_v1.5$ channel expression varies in the different regions of the heart, showing a high level of expression in the specialized conduction system, atria and ventricles, while being absent in the central sinus and atrioventricular nodal tissues (FIGURE 5). Also, $\text{Na}_v1.5$ channels gather in clusters and associate with accessory subunits and partner proteins, forming region-specific macromolecular complexes (95). They are not evenly distributed within the myocyte (96). The current densities are large in the intercalated disk area and smaller in the lateral membrane (96, 97). The complex nature and the observed regional differences in sodium channel expression, as well as the functional significance of $\text{Na}_v1.5$ interactions with partner proteins, justify further studies to better understand the pathophysiology of diseases associated with $\text{Na}_v1.5$ dysfunction, including inherited sodium channelopathies (94, 98).

The function of I_{Na} is regulated by intracellular calcium homeostasis in a complex way that involves multiple

accessory proteins (99). Calmodulin (CaM), the ubiquitous Ca^{2+} -sensing protein, plays a central role in intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$)-dependent I_{Na} function alterations by modulating fast inactivation of I_{Na} (100). Recent data suggest that CaM facilitates the recovery of the sodium channel from inactivation by interacting with its inactivation gate in a Ca^{2+} -dependent fashion (101). The different binding sites of CaM on the sodium channel are important to understand the mechanisms linked to disease-associated sodium channel mutations (102–104). In addition to CaM, Ca^{2+} /calmodulin-dependent kinase II (CaMKII) has been shown to modify I_{Na} function in a Ca^{2+} -dependent manner. CaMKII phosphorylation regulates cardiac Na^+ channels by slowing their recovery from inactivation (105, 106). This results in reduced availability of fast I_{Na} at a high rate with enhanced late I_{Na} (106). The latter contributes to prolonged repolarization and enhanced arrhythmia susceptibility (106, 107) often seen in heart failure, where CaMKII activity is enhanced (107).

In addition to TTX, I_{Na} is blocked, although not selectively, by a wide range of antiarrhythmic drugs, e.g., lidocaine, mexiletine, quinidine, disopyramide, and

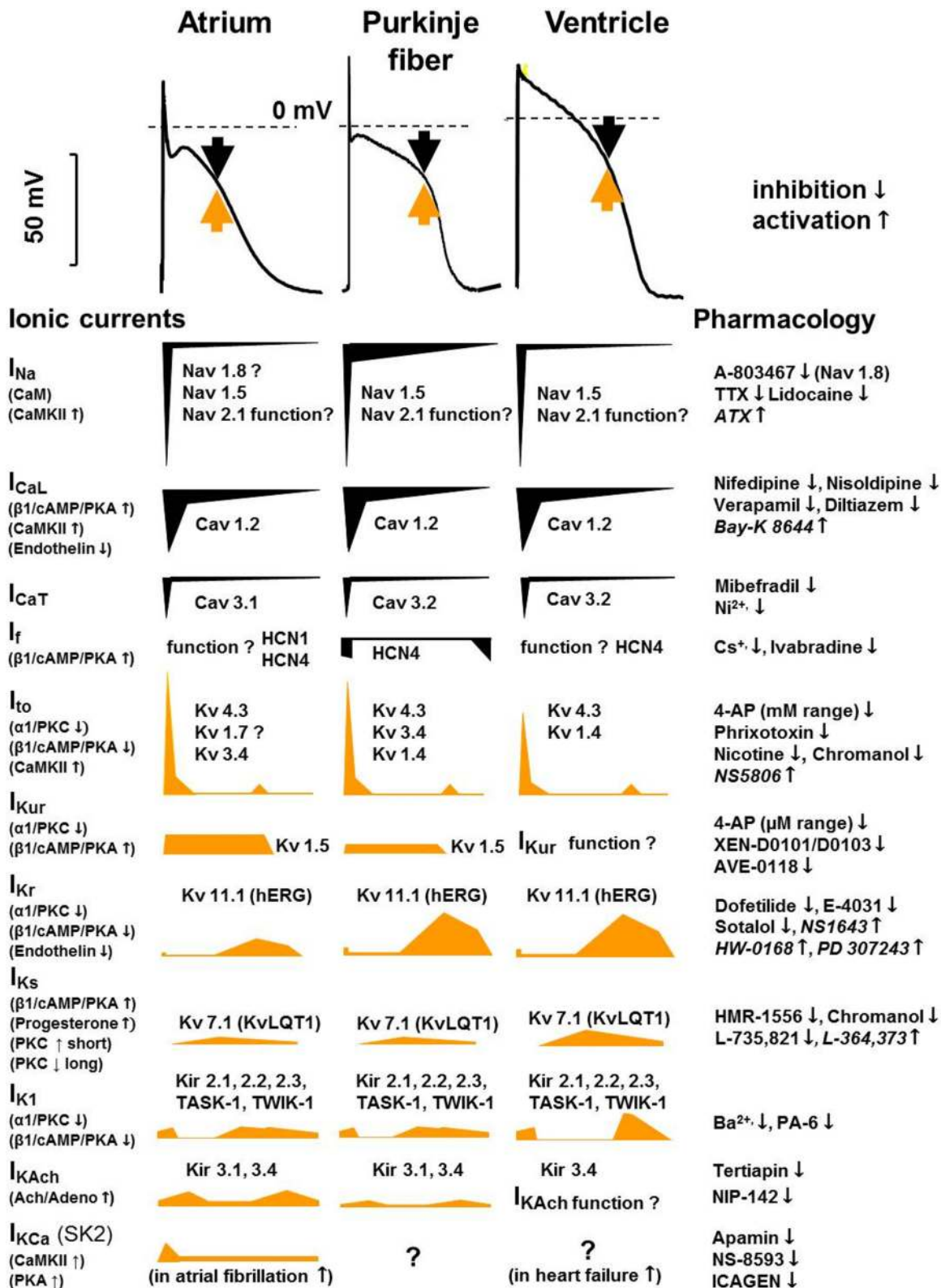


FIGURE 6. Tissue-specific (human) cardiac atrial, Purkinje fiber, and ventricular action potentials and the underlying ionic currents in different action potential phases, indicating their pharmacology and modulation. Black arrows indicate inward and yellow arrows indicate outward current. The contributions of different currents to the action potentials are indicated below, with a time course adjusted to the action potential. CaM, calmodulin; CaMKII, Ca²⁺-calmodulin kinase II; hERG, human ether-à-go-go-related gene; *I_{K1}*, inward rectifier potassium current; *I_{KAch}*, acetylcholine-activated potassium current; *I_{Na}*, sodium current; *I_{CaL}*, L-type calcium current; *I_{CaT}*, T-type calcium current; *I_f*, funny/pacemaker current; *I_{to}*, transient outward current; *I_{KCa}*, calcium-activated potassium current; *I_{Kr}*, *I_{Ks}*, and *I_{Kur}*, rapid, slow, and ultrarapid components of delayed rectifier potassium current; *K_r*, inward rectifier potassium channel; *K_v*, voltage-gated potassium channel; *Nav_v*, voltage-gated sodium channel; TASK, Tandem of pore domains in a weak inward rectifying potassium channel (TWIK)-related acid-sensitive potassium channel; TTX, tetrodotoxin.

flecainide (FIGURE 6) (108, 109) in a frequency-dependent manner. It has recently been reported that certain drugs like ranolazine and GS967 selectively inhibit I_{NaLate} (110, 111). Therefore, these compounds would be particularly effective for long QT (LQT) syndromes, heart failure (HF), or hypertrophic cardiomyopathy (HCM) (110). On the other hand, late I_{Na} can be pharmacologically augmented by veratrine (112), veratridine, and ATX (113).

Genetic mutations that alter I_{Na} function can lead to severe, potentially lethal, conditions and have been shown to play a significant role in a wide array of inherited channelopathies (for recent reviews see Refs. 94, 114–117). As an example, loss-of-function *SCN5A* mutations lead to a reduced I_{Na} peak, thus slowing impulse conduction and possibly causing conduction block. These mutations have been identified in ~20% of patients with Brugada syndrome (BrS) (118) as well as in patients with sick sinus syndrome and progressive cardiac conduction defect (119–121). On the other hand, gain-of-function *SCN5A* mutations have been shown to play key roles in congenital LQT3 syndrome (122). In some cases of familial AF, both loss-of-function and gain-of-function *SCN5A* mutations have been identified (123, 124).

The late sodium or window current, irrespective of its basic mechanism or molecular background, is particularly important in arrhythmogenesis (125). As an example, in HF and in HCM, I_{NaLate} is augmented (126, 127). Since this current is an important contributor to the action potential plateau phase, its enhancement prolongs repolarization and increases repolarization heterogeneity (110, 128). In addition, by increasing intracellular sodium concentration, it also increases intracellular calcium concentration, via the $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX). This can evoke arrhythmogenic triggered activity such as early and delayed afterdepolarizations (EADs and DADs, respectively) (129–131), discussed below in this review. Both triggered automaticity and enhanced dispersion of repolarization are considered major mechanisms in arrhythmogenesis, and their reduction is a major aim in antiarrhythmic drug development.

3.2. The Transient Outward Current

The main channels providing the transient outward potassium current (I_{to}) in human and dog ventricular muscle are $\text{K}_v4.3$ and $\text{K}_v4.2$ pore-forming α -subunits coassembled with KChIP2 and DPP auxiliary subunits (85) encoded by *KCND3*, *KCND2*, and *KCNIP2* and *DPP6/10* genes, respectively (132–134). $\text{K}_v1.4$ α channel subunits (encoded by *KCNA4*) are also expressed with marked regional and interspecies dependence, making up ~10–20% of I_{to} density in humans (135, 136). Accordingly, in humans (unlike in dogs), in addition to the rapid

component ($\tau_{\text{fast}} \sim 50\text{--}100$ ms), the I_{to} recovery from inactivation also has a component with a slow recovery time constant (on the order of seconds) that is characteristic of the $\text{K}_v1.4$ channels (137). It is interesting that in rabbit ventricle the I_{to} current is primarily conducted by $\text{K}_v1.4$ channels (138). However, the functional role of this channel in rabbits is still unclear, as it is inactivated most of the time at their physiological heart rate, which is quite high. In humans, both $\text{K}_v4.3$ and $\text{K}_v1.4$ channels can have functional roles, particularly in the frequency-dependent modulation of the APD during both different constant or following abrupt changes in cycle lengths during electrical restitution (i.e., following extrasystoles with different coupling intervals). In addition, there are mRNA expression studies (85, 139) supporting the possibility that the $\text{K}_v1.7$ channels also have a functional role for I_{to} in human atria and ventricles. However, because of the relative paucity of data regarding $\text{K}_v1.7$ channels in the heart, further research is needed to properly elucidate these issues.

Human and dog I_{to} start activating at membrane potentials more positive than -30 mV, rapidly reaching peak values (within 1–2 ms) and then inactivating with a double-exponential time course ($\tau_{\text{fast}} \sim 5$ ms, $\tau_{\text{slow}} \sim 25$ ms) (140). The $\text{K}_v4.3$ channel-mediated I_{to} , unlike $\text{K}_v1.4$, recovers rapidly from inactivation in the membrane voltage range of -60 to -80 mV, with a time constant of ~ 50 ms (137). In dog and human Purkinje fibers, $\text{K}_v3.4$ channels were also described to contribute to I_{to} , with different kinetic properties compared with $\text{K}_v4.3$ channels (141). This raises the possibility for fine-tuning of frequency-dependent modulation of repolarization dispersion between Purkinje fibers and ventricular muscle (142).

The transient outward potassium current and the fast inactivation of I_{Na} are important contributors to the early/fast repolarization of the action potential (phase 1) (137, 143) (FIGURE 4). Phase 1 repolarization and I_{to} are more prominent in Purkinje fibers and atrial, mid-myocardial, and subepicardial ventricular muscle (137), but they are small, or nonexistent, in subendocardial ventricular cells and sinoatrial (SA) and atrioventricular (AV) nodal cells (137). Interestingly, phase 1 repolarization and I_{to} are not present in guinea pig ventricular myocytes (144, 145). Also, it has been reported that in mouse ventricle I_{to} is small and action potential is long after birth and later the action potential shortens as I_{to} develops in adult mice (146, 147). The impact of I_{to} on the shape of the action potential waveform is complex. In addition to its role in phase 1, I_{to} also modulates the voltage level of the plateau, and consequently it has an indirect influence on activation, inactivation, and deactivation of several other transmembrane ionic currents that operate during the plateau phase. Since I_{to} ,

similarly to I_{Na} , has activation, deactivation, and inactivation properties, it was also suggested that a window I_{to} current may be generated, in the membrane potential range from -35 to -10 mV. This window current would also contribute to the final repolarization (140). It was also reported that interaction of DPP10a with $K_v4.3$ channels results in a sustained current component of human atrial I_{to} that can participate in the late repolarization phase (148). However, despite its potential importance, it is difficult to validate or disprove the existence of such current, since selective inhibitors are lacking. This suggests the need for further research to clarify this issue. I_{to} is a typical transmembrane ionic current that can be attributed to the function of a wide variety of distinctly different potassium and also chloride ion channels (137). Although the role of I_{to} in arrhythmias is not well defined, it definitely plays a role in Brugada syndrome (117, 149), where a reduced expression level of the auxiliary I_{to} subunit, KChIP2, in females most likely underlies the male phenotypic predominance (150, 151). The stronger epicardial I_{to} in males could further aggravate the consequence of impaired I_{Na} in Brugada patients; in this case, inhibition of I_{to} would be beneficial. Multiple nonselective I_{to} inhibitors have been reported (FIGURE 6): 4-aminopyridine (4-AP), in millimolar concentrations (152); quinidine, flecainide, and chromanol 293B, in micromolar concentrations (140, 152); and phrixotoxin, in nanomolar concentrations (153). However, a selective I_{to} inhibitor is still lacking. This could constitute a potential treatment in atrial fibrillation, by increasing APD and consequently ERP, in atrial but not or less in ventricular tissue (154). An activator for I_{to} was also reported having effect on canine ventricular but not atrial myocytes (155).

I_{to} is downregulated in HF (156–159), HCM (160), and diabetes mellitus (161, 162), possibly contributing to repolarization prolongation in these pathological settings. Recently, it was shown that $K_v4.3$ (fast I_{to}) and $K_v1.4$ (slow I_{to}) were expressed differently in normal and failing hearts, thus contributing to arrhythmogenic regional heterogeneity in action potential waveforms (101). It was also demonstrated that a slowing of phase 1 repolarization, which can be due to the decreased I_{to} often observed in failing hearts (163–165), decreases the driving force of Ca^{2+} through L-type calcium channels, and it can result in potentially arrhythmogenic asynchronous Ca^{2+} release from the sarcoplasmic reticulum (SR) (166). I_{to} is subject to α - and β -adrenergic regulation, both decreasing I_{to} via the PKA and PKC pathways (167), whereas CaMKII has been shown to increase I_{to} (167).

Thyroid-stimulating hormone and thyroid hormones have been shown to modulate I_{to} (168, 169), thus making

I_{to} an important contributor to repolarization abnormalities in altered thyroid status.

3.3. Inward Calcium Current

The inward calcium current (I_{Ca}) in the heart was first described by Reuter (170), and it has two major types (171, 172). The most abundant type is the L-type calcium channel ($Ca_v1.2$), which conducts current through the pore-forming α -subunit (α_1) encoded by the *CACNA1C* gene (85). The α_1 -subunit consists of $\sim 2,000$ amino acids, organized into four repeat domains (I–IV), each containing six transmembrane segments (S1–S6) (173). The S4 transmembrane helix from each domain collectively constitute the voltage sensor of the channel (173). A region called the “P loop” connecting the S5 and S6 segments is responsible for the Ca^{2+} selectivity of the pore region (174). The pore-forming subunit coassembles with the extracellular $\alpha_2\delta$ and intracellular β auxiliary (predominantly β_2 in cardiac tissue) subunits that modulate kinetics, gating, and trafficking properties of the channel (175–177). Inward L-type Ca^{2+} current ($I_{Ca,L}$) has a very rapid activation (14) and is particularly important for excitation-contraction coupling (178), since it serves as a trigger for the calcium-induced calcium release (CICR) (179) from the SR and as a source of extracellular calcium when needed. In addition, $I_{Ca,L}$ plays a fundamental electrophysiological role in maintaining the plateau phase of the action potential (FIGURE 4) and in the depolarization of SA and AV nodal cells (180). In these cell types, $I_{Ca,L}$ is the main contributor to impulse conduction; therefore its impairment prolongs the PQ interval and can result in AV node conduction block. In addition, since $I_{Ca,L}$ provides depolarizing current, its decrease would reduce the spontaneous frequency of these cells. In AV nodal cells, this shift in threshold potential also contributes to the slowing of AV impulse conduction. The inactivation kinetics of L-type I_{Ca} ($\tau_{fast} \sim 2\text{--}8$ ms, $\tau_{slow} \sim 30\text{--}100$ ms) depend not only on membrane voltage but also on the intracellular Ca^{2+} concentration (14, 15, 181–184), which is dynamically changing during the action potential. The recovery from inactivation is complex and strongly depends on voltage. At -40 mV it can be characterized by an exponential time course ranging between 30 and 60 ms with $\tau_{fast} = \tau_{slow}$ (14, 185). Importantly, the recovery kinetics can be faster in ventricular and Purkinje fibers, which have a resting potential around -80 mV. The $I_{Ca,L}$ was originally called slow inward current (I_{si}), since with the old experimental methods, before the introduction of single-cell voltage clamp, a relatively slow I_{Ca} activation was measured (170, 186). Later, with more advanced voltage-clamp techniques, the proper fast activation kinetics could be determined (187).

Table 1. Changes of genes, channel/transporter proteins, and ionic currents in various genetic disorders

Genetic Disorder	Gene	Protein	Ionic Current/Function
<i>Trigger</i>			
CPVT 1	<i>RYR2</i>	Ryanodine receptor	SR Ca ²⁺ release
CPVT2	<i>CASQ2</i>	Calsequestrin	↑ SR Ca ²⁺ release
Inherited sinus bradycardia	<i>SCN5A</i>	Na _v 1.5	↓ I _{Na}
Sick sinus syndrome	<i>HCN4/SCN5A</i>	HCN4/Na _v 1.5	↓ I _f /I _{Na}
Familial inappropriate tachycardia	<i>HCN4/SCN5A</i>	HCN4/Na _v 1.5	↑ I _f /I _{Na}
<i>Substrate</i>			
Brugada syndrome	<i>SCN5A</i>	Na _v 1.5	↓ Impulse conduction
ARVC (Naxos disease)		Desmosome protein	↓ Impulse conduction
LQT1	<i>KCNQ1</i>	KCNQ1 (Kv7.1)	↓ I _{Ks}
LQT2	<i>KCNH2</i>	hERG (Kv11.1)	↓ I _{Kr}
LQT3	<i>SCN5A</i>	Na _v 1.5	↑ I _{Na}
LQT4 (ankyrin-B syndrome)	<i>ANK2</i>	Ankyrin-B	Multichannel interactions
LQT5	<i>KCNE1</i>	KCNE1 (minK)	↓ I _{Ks}
LQT6	<i>KCNE2</i>	KCNE2 (MiRP1)	↓ I _{Kr}
LQT7 (Andersen–Tawil syndrome type 1)	<i>KCNJ2</i>	K _{ir} 2.1	↓ I _{K1}
LQT8 (Timothy syndrome)	<i>CACNA1C</i>	Ca _v 1.2	↑ I _{Ca}
LQT9	<i>CAV3</i>	Caveolin 3	↑ I _{Na}
LQT10	<i>SCN4B</i>	Na _v 1.5 β4	↑ I _{Na}
LQT11	<i>AKAP9</i>	AKAP-9 (yotiao)	↓ I _{Ks}
LQT12	<i>SNTA1</i>	α1-Syntrophin	↑ I _{Na}
LQT13	<i>KCNJ5</i>	K _{ir} 3.4 (GIRK4)	↓ I _{KACH}
LQT14	<i>CALM1</i>	Calmodulin	Multichannel interactions
LQT15	<i>CALM2</i>	Calmodulin	Multichannel interactions
LQT16	<i>CALM3</i>	Calmodulin	Multichannel interactions
SQT1	<i>KCNH2</i>	HERG	↑ I _{Kr}
SQT2	<i>KCNQ1</i>	KVQT1	↑ I _{Ks}
SQT3	<i>KCNJ2</i>	K _{ir} 2.1	↑ I _{K1}
SQT4	<i>CACNA1C</i>	Ca _v α1	↓ I _{Ca,L}

Continued

Table 1.—Continued

Genetic Disorder	Gene	Protein	Ionic Current/Function
SQT5	<i>CACNB2b</i>	Ca _v β2b	↓ <i>I</i> _{Ca,L}
SQT6	<i>CACNA2D1</i>	Ca _v α(2) δ-1	↓ <i>I</i> _{Ca,L}
SQT7	<i>SLC22A5</i>	OCTN2	Carnitine deficiency
SQT8	<i>SLC4A3</i>	AE3	↓ Cl ⁻ /HCO ₃ ⁻ exchanger function
Familial AF	<i>KCNQ1</i>	K _v LQT1	↓ <i>I</i> _{Ks}
	<i>KCNE2</i>	MIRP1	↓ ?
	<i>KCNJ8</i>	K _{ir} 6.1	↑ <i>I</i> _{K,ATP}

AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; CPVT, catecholaminergic polymorphic ventricular tachycardia; *I*_{Ca}, calcium current; *I*_{Ca,L}, L-type Ca²⁺ current; *I*_f, funny/pacemaker current; *I*_{K,ACH}, acetylcholine-activated potassium current; *I*_{K,ATP}, ATP-sensitive potassium current; *I*_{Kr}, rapid component of delayed rectifier potassium current; *I*_{Ks}, slow component of delayed rectifier potassium current; *I*_{K1}, inward rectifier potassium current; *I*_{Na}, sodium current; LQT, long QT syndrome; SQT, short QT syndrome; SR, sarcoplasmic reticulum.

*I*_{Ca,L} is modulated (FIGURE 6) by cAMP-dependent phosphorylation and other factors, including intracellular Ca²⁺ levels (15). It has been shown that CaM supports both inactivation and facilitation of *I*_{Ca} (188). The intracellular Ca²⁺ enhances *I*_{Ca} via CaMKII, involving direct phosphorylation of L-type Ca²⁺ channels (189, 190) independently of cAMP via PKA (191) involving Rad, a monomeric G protein that closely interacts with Ca_v1.2 (192). *I*_{Ca,L} can be effectively blocked (FIGURE 6) by Cd²⁺, verapamil, and diltiazem, but the inhibition with these drugs is not selective (193–195). Dihydropyridines, e.g., nifedipine (196) and nisoldipine (197), are more selective *I*_{Ca,L} blockers, but they may be sensitive to light (198). Pharmacological activation of *I*_{Ca,L} is also possible by Bay K8644 (FIGURE 6) (199).

The *I*_{Ca,L} has key roles in several diseases like HF (200), HCM (27), AF (201), and myocardial ischemia and in other pathophysiological conditions, such as the development of EADs, DADs, (202–204) and cardiac ischemia-reperfusion (205), discussed in more detail in other parts of this review.

A gain-of-function G406R mutation of the Ca_v1.2 channel causes type 8 of congenital LQT syndrome, also called Timothy syndrome (TABLE 1). This disease is characterized by slower inactivation of *I*_{Ca,L} (206–208) and by the fact that small clusters of Ca_v1.2 channels have a larger probability for coordinated opening and closing (“coupled gating”) (209), thus leading to tachyarrhythmia and congenital heart defects (ductus arteriosus, ventricular septal defect, Fallot tetralogy, HCM) (210).

The second type is the T-type calcium current (*I*_{Ca,T}), for which significantly less data are available. Its functional role in atrial and ventricular cells and Purkinje

fibers is still unclear. However, it plays an important role in the SA and AV nodal cells (211), where it makes a significant contribution to the pacemaker function. This current is conducted by Ca_v3.1 and Ca_v3.2 channels, encoded by *CACNA1G* and *CACNA1H* genes, respectively (212). *I*_{Ca,T} activates at more negative membrane potentials than *I*_{Ca,L}, and its overlap with *I*_{Na} makes it difficult to study (172). *I*_{Ca,T} can be inhibited by low concentrations (100–200 μM) of Ni²⁺ (172) and by the organic compound mibefradil, which was developed with the aim of decreasing elevated heart rate (213).

3.4. Delayed Rectifier Potassium Currents

Before the introduction of the patch-clamp technique, a slowly activating current carried by K⁺ was recorded during the plateau phase. This current was named the delayed rectifier potassium current (*I*_{x/2}). Later, by applying single-cell patch-clamp technique, Sanguinetti and Jurkiewicz (214) showed that this delayed rectifier outward potassium current can be separated into a rapid (*I*_{Kr}) and a slow (*I*_{Ks}) component. Molecular biological studies also confirmed that these two *I*_K components are conducted by distinctly different ion channels.

3.4.1. The rapid delayed-rectifying potassium current.

The rapid delayed rectifier outward potassium current (*I*_{Kr}) is conducted by the K_v11.1 pore-forming α-subunit, also called hERG in humans (human ether-à-go-go related gene), which is associated with various accessory β and possibly other subunits (85, 215, 216).

Similarly to other K_v channel pore-forming α -subunits, $K_v11.1$ consists of six transmembrane segments (S1–S6) and the functional channel contains four α -subunits (FIGURE 3) (217). The $K_v11.1$ hERG α -subunit has two isoforms (a and b), which are different in terms of gating and drug sensitivity (65, 66). The wide variety of interacting accessory β -subunits include MinK (human minimal potassium ion channel), MiRP1 (mink-related peptide 1), and MiRP2, MiRP3, and MiRP4 proteins encoded by *KCNE1*, *KCNE2*, *KCNE3*, *KCNE4*, and *KCNE5* genes, respectively (85, 215). Initially, it was suggested that MiRP1 interacted with hERG ($K_v10.1$) to form I_{Kr} channels (218). This is due to the fact that when hERG ($K_v11.1$) α channel subunits were expressed alone in HEK cells, a very rapidly activating steady-state-like current was observed, and only coexpression with MiRP1 resulted in currents that resembled native I_{Kr} . On the basis of this observation MiRP1 was considered the most important accessory subunit to form the native I_{Kr} channel. However, later studies indicated very low levels of *KCNE2* expression in human heart, whereas genes of

other β -subunits like MinK, MiRP2, MiRP3, and MiRP4 were abundantly expressed in human atrial and ventricular tissue and Purkinje fibers (85). Coexpression of the β - and hERG α -subunits produced currents with kinetics similar to those native currents that can be recorded in different species including human (219, 220). However, the exact role of these β and other possible accessory subunits, how they regulate I_{Kr} , and whether they are responsible for the observed species-dependent differences and drug sensitivities are unclear at present and need to be elucidated in the future. I_{Kr} activates in a voltage-dependent manner, with an activation τ of 31 ms at +30 mV in human ventricular myocyte (221). It also slowly deactivates (222) in a voltage-dependent manner; its deactivation can be fitted by a double exponential with τ_{fast} of 600 ms and τ_{slow} of 6,800 ms at –40 mV. The ratio of the amplitudes of the fast and slow components increases at more negative potentials. I_{Kr} exhibits a peculiar, very rapid, inactivation (223–225), which starts even before it activates.

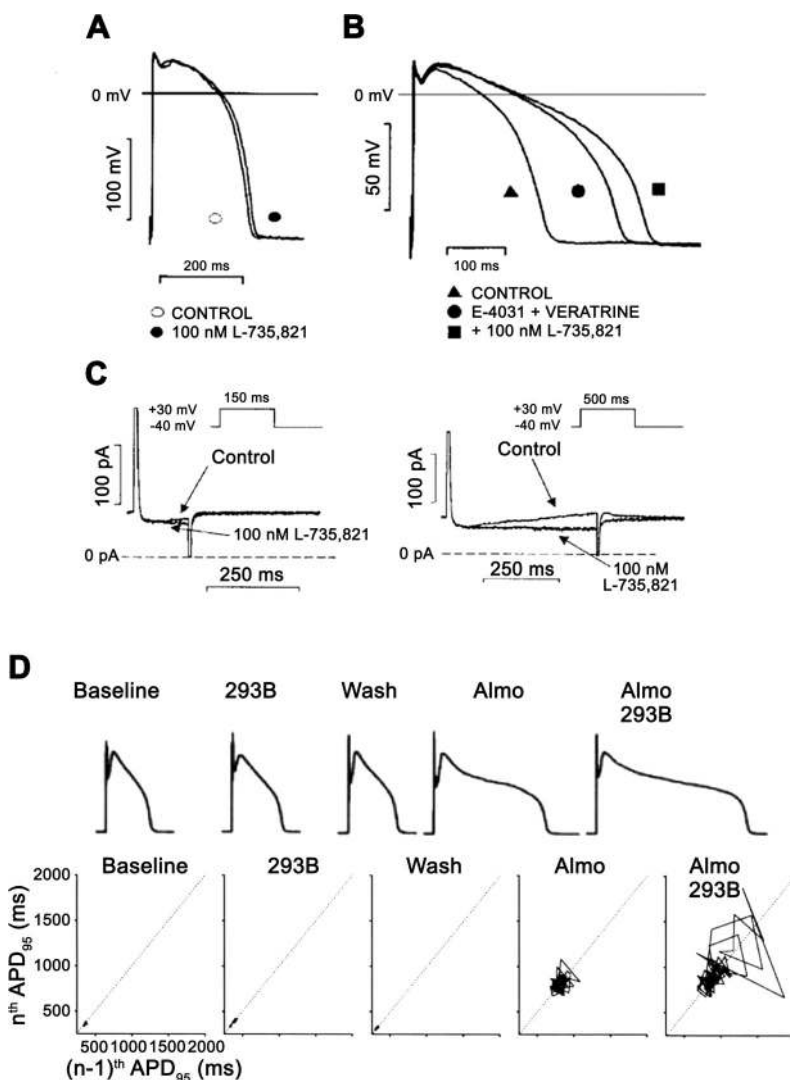


FIGURE 7. The role of the slow component of the delayed rectifier potassium current (I_{Ks}) in the repolarization in dog ventricular papillary muscle (A–C) and in dog single ventricular myocyte (D). In A, action potential duration (APD) is not, or minimally, changed after full I_{Ks} inhibition by 100 nM L-735,821 without external sympathetic stimulation. In B, in the same preparation full I_{Ks} inhibition elicited significant prolongation of repolarization in a preparation where the rapid component of the delayed rectifier potassium current (I_{Kr}) was inhibited by E-4031 and late sodium current (I_{NaLate}) was augmented by veratrine. In C, transmembrane current recordings show that during a short (150 ms) voltage pulse very little I_{Ks} develops, but when pulse duration was increased to 500 ms significant I_{Ks} developed, explaining the lack and significant changes of APD after I_{Ks} inhibition in A and B. (Reproduced from Ref. 228 with permission.) In D, the result of a representative experiment is shown in dog ventricular myocytes. In the baseline (control) situation, small short-term APD variability and normal APD were recorded that did not change significantly after I_{Ks} inhibition by chromanol 293B. Additional application of I_{Kr} block by almokalant increased both APD and short-term APD variability illustrated by the Poincaré plot, which was substantially further lengthened and increased by additional I_{Ks} inhibition, respectively. (Reproduced from Ref. 255 with permission.)

During the action potential in early plateau and in phase 3, I_{Kr} channels rapidly recover from inactivation and they reopen as voltage changes toward more negative values, and deactivation progresses. Accordingly, despite the rapid activation of the current during the plateau phase, a relatively tiny current develops that gradually increases and decreases during phase 3 repolarization (FIGURE 4); therefore it is a crucially important current to secure repolarization.

Since I_{Kr} deactivates slowly, it does not have time to fully deactivate during an action potential. Therefore, a residual and gradually decreasing outward current can still flow through this channel, thus shortening the next action potential when diastolic interval is relatively short, i.e., during fast heart rate or during an early extrasystole (222). Consequently, I_{Kr} is considered a key player in frequency-dependent APD regulation, and it can influence the pacemaker function as well (226).

I_{Kr} can be blocked by specific compounds in the submicromolar or micromolar range (e.g., dofetilide and E-4031) (FIGURE 13 and FIGURE 7), causing a marked prolongation of the action potential (227, 228). It was reported that this current can be modulated (FIGURE 6) by endogenous substances like endothelin, which suppresses I_{Kr} (229). Decreased I_{Kr} was also observed after α_1 - and β_1 -receptor activation, linked to the PKC and PKA pathways, respectively (230–232). There are also some compounds known to enhance I_{Kr} (FIGURE 6).

In pathophysiological conditions, I_{Kr} can change. In hypokalemia, the magnitude of the current decreases (233–235), thus making the heart vulnerable to torsades de pointes (TdP) arrhythmia, especially in the presence

of I_{Kr} -blocking drugs (236). The effect of ischemia on I_{Kr} is complex, since acidosis was reported to decrease I_{Kr} (237, 238), particularly by inhibition of the hERG1b isoform of the channel (239), but hyperkalemia can increase (234, 235) the current—and both are present in ischemia. Reduced I_{Kr} was also reported in the infarcted zone in dog myocytes (240). In HF, I_{Kr} is generally considered downregulated (241), even if different studies report sometimes contradictory results.

Loss-of-function mutations in hERG channel can cause congenital long QT syndromes (237, 242, 243), whereas gain-of-function mutations lead to short QT syndromes (244–246) (TABLE 1).

3.4.2. The slow delayed-rectifying potassium current.

The slow component (I_{Ks}) of I_K is carried by the $K_v7.1$ channel, consisting of a pore-forming α -subunit (FIGURE 3) (217), encoded by the *KCNQ1* gene, that coassembles with various MinK, MiRP1, MiRP2, MiRP3, MiRP4, and other accessory subunits, encoded by *KCNE1*, *KCNE2*, *KCNE3*, *KCNE4*, and *KCNE5* genes, respectively (85, 215). MinK was the first β accessory protein (247, 248) that was identified for the $K_v7.1$ channel, but later the importance of other β -subunits (e.g., MiRP1, MiRP2, MiRP3, MiRP4) was recognized, suggesting that this variability in β -subunits may serve as the basis for the marked interspecies variability in native I_{Ks} properties (67, 68). In guinea pig, the amplitude of I_{Ks} is large [(3, 214, 249), and its kinetics differs from those measured in rabbit (250, 251), dog (228) or human (252, 253) ventricular muscle. In

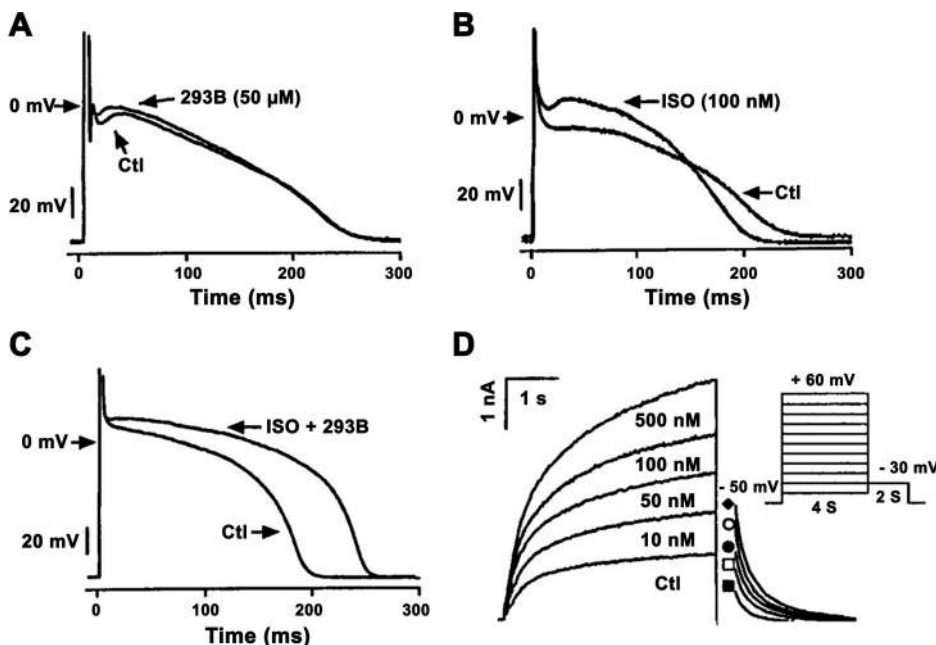


FIGURE 8. A–C: influence of slow component of delayed rectifier potassium current (I_{Ks}) inhibition by chromanol 293B (A), sympathetic stimulation by isoproterenol (ISO, B), and combination of I_{Ks} block and sympathetic stimulation (C) in isolated dog cardiac Purkinje cells. Note that in control (Ctl) condition plateau phases of the Purkinje cells are at more negative voltage than the activation threshold of I_{Ks} , and accordingly I_{Ks} inhibition did not change repolarization. In B, isoproterenol shifted the action potential plateau voltage to more positive values because of substantially increased I_{Ks} . D: in this situation, I_{Ks} inhibition substantially lengthened repolarization as shown in C. (Reproduced from Ref. 157 with permission.)

most species, I_{K_S} activates slowly and in a voltage-dependent manner, at potentials more positive than -30 mV, with τ of several hundred milliseconds to seconds (254). The current deactivates rapidly, except in guinea pigs, in a voltage-dependent manner, with τ of <200 ms at -40 mV (253). The density of I_{K_S} during the plateau of a normal action potential is small (FIGURE 4), because of its slow activation. Therefore, its contribution to repolarization without β -adrenergic stimulation is minimal, except in guinea pig (FIGURE 7A). However, normal physiological conditions always involve some level of sympathetic tone that increases basal I_{K_S} density (255). In addition, when plateau voltage is enhanced by the elevated sympathetic tone, more I_{K_S} develops and contributes more to repolarization (256) (FIGURE 8). I_{K_S} is a critical contributor to the repolarization reserve (257, 258). According to this concept, cardiac repolarization is provided by multiple redundant ionic currents that can compensate for each other's loss of function. Therefore, a dysfunction of a single repolarizing current does not necessarily cause a measurable effect on repolarization. However, congenital or acquired defects in the function of multiple currents can be additive. As shown in FIGURE 7, A and D, I_{K_S} block at baseline does not prolong ventricular repolarization and does not increase short-term variability of APD, which is a recently suggested predictive parameter of proarrhythmic risk (259). However, after I_{K_r} block (by E-4031 or almokalant), I_{K_S} inhibition significantly prolongs repolarization (FIGURE 7B) and increases short-term variability of repolarization. At longer repolarization duration, induced either by I_{K_r} block or by longer voltage pulses (FIGURE 7, B and C), more I_{K_S} develops and, as a negative feedback mechanism, it can limit excessive APD lengthening (221, 228, 260). Although some studies have reported I_{K_S} in atrial tissue (261, 262), and both KCNQ1 and its accessory subunits are expressed in the atria at levels similar to those in the ventricle (263), the presence and role of I_{K_S} in human and canine atrial including sinoatrial node (SAN) cells are still unclear. Assuming similar I_{K_S} kinetics in atria and ventricles, less I_{K_S} activation can be expected in atrial myocytes, since the plateau phase is shorter and it develops at more negative voltages than in ventricular myocytes. One may speculate that at very rapid rates (e.g., during atrial fibrillation or flutter) the continuous presence of a very tiny I_{K_S} current during the action potential, due to frequent channel opening and slow recovery compared with the diastolic interval, may produce a steady-state-like sustained outward current, which may have a role in modulating the resting membrane potential, the pacemaker activity, or even the APD. To resolve these controversies, further research is needed.

I_{K_S} is regulated by endogenous substances (FIGURE 6). Progesterone, and cAMP/PKA-dependent phosphorylation via the Yotiao accessory subunit protein (264), increases I_{K_S}

(255, 265). PKC has a biphasic influence, increasing I_{K_S} after short-term application and decreasing I_{K_S} after long-term application (266). It was also reported that the PKC-mediated I_{K_S} augmentation was PKC isoform dependent (267, 268). Drugs are available to inhibit (228) and to activate (269) I_{K_S} (FIGURE 6). Hypokalemia and elevated intracellular Ca^{2+} enhance and hyperkalemia decreases I_{K_S} (235, 270).

Diseases like heart failure (7) and diabetes mellitus (271) and genetic mutations (LQT1) (114, 149) or drugs (228) can reduce I_{K_S} channel expression, and, as a consequence, the reserve repolarizing current provided by I_{K_S} would be diminished.

This scenario can be further aggravated when intracellular cAMP is elevated, and cAMP-dependent phosphorylation enhances L-type I_{Ca} . Since $I_{Ca,L}$ is an inward current, which prolongs repolarization, the negative feedback function of impaired I_{K_S} cannot sufficiently limit excessive APD prolongation. Therefore, dispersion of repolarization and propensity for life-threatening arrhythmia can increase (272). Genetic mutations can also lead to gain of function of I_{K_S} , resulting in increased current. The mutations have been shown to have concomitant effects in sinoatrial, ventricular, and atrial cardiomyocytes and lead to complex clinical phenotypes (273–281).

3.5. Inward Rectifier Potassium Current

Inward rectifier potassium current (I_{K1}), similarly to I_{to} , is a current that is carried by several channels (282), even if this fact is sometimes overlooked when its behavior is discussed (283). Therefore, the definition of I_{K1} needs

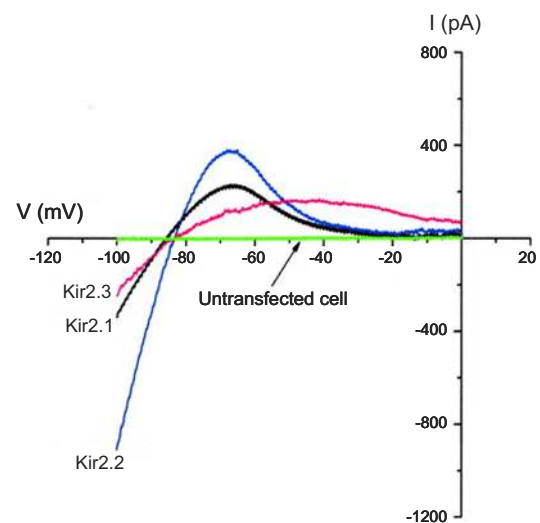


FIGURE 9. Distinct current (I -voltage (V) relations of inward rectifier potassium (K_{ir}) $2.x$ channels expressed in HEK293 cells. Different colors depict ramp (-100 to 0 mV)-generated, barium-sensitive currents in cells expressing $K_{ir}2.x$ channels. The current in an untransfected cell is shown in green. (Reproduced from Ref. 63 with permission.)

particular care. Here we define I_{K1} as a current conducted by channels consisting of $K_{ir}2.1$, $K_{ir}2.2$, $K_{ir}2.3$, and $K_{ir}2.4$ pore-forming α -subunits, encoded by *KCNJ2*, *KCNJ12*, *KCNJ4*, and *KCNJ14* genes, respectively (215, 282). Four α -subunits (each containing 2 transmembrane segments, S1 and S2) combine to form the tetrameric, functional K_{ir} channel (FIGURE 3) (217). I_{K1} channels may also have other, as yet undefined, accessory subunits. Remarkable differences have been observed between currents flowing through the different K_{ir} channel isoforms (63) expressed in mammalian cell lines (FIGURE 9), thus raising the possibility that different species and cardiac tissue types express different channel isoforms, with various phenotypes. Further research will elucidate the exact roles of different K_{ir} channel isoforms.

I_{K1} is considered one of the most important currents securing the resting membrane potential and shaping terminal repolarization in phase 3 of the action potential (FIGURE 4). According to classical electrophysiological principles, one would expect potassium channels to conduct current more easily in the outward direction, as the intracellular K^+ concentration is much greater than the extracellular. Instead, inward rectification means that the steady-state current decreases at potentials positive to about -50 mV. This inward rectification was attributed to channel inactivation caused by intracellular Mg^{2+} and polyamines (284, 285). At potentials more negative than the K^+ reversal potential, I_{K1} is an inward current that has a rapidly inactivating component (286) negative to -120 mV, but the physiological importance of this inactivation has not been established. This current is regularly measured as a Ba^{2+} -sensitive steady-state current at the end of voltage pulses (287). However, Ba^{2+} is not fully selective for any of the K^+ channels described so far, and the steady-state current-voltage relation measured can also include other, not well-characterized, currents, described as “leak” or “plateau” currents (I_{leak} or I_p , respectively) (4, 283, 288).

There are reports suggesting that intracellular $[Ca^{2+}]$ changes can modulate I_{K1} (287, 289, 290), possibly relevant to frequency-dependent APD regulation or in certain pathological settings (291). I_{K1} is also increased by elevated extracellular K^+ concentration ($[K^+]_o$) (292, 293). Hyperkalemia increases I_{K1} by electrostatically destabilizing Mg^{2+} - and polyamine-induced I_{K1} block by displacing these cations from their binding sites (294).

Activation of both the $\alpha_1/$ PKC and $\beta_1/$ PKA pathways have been shown to reduce I_{K1} in human isolated cardiomyocytes (295, 296). A similar effect of neurokinin-3 was observed on I_{K1} in rabbit and human atria (297). These results further emphasize the importance of autonomic control of atrial APD and electrical function. I_{K1} can be inhibited (FIGURE 6) by Ba^{2+} in the micromolar range (140) and

by the organic compound PA-6 in the nanomolar range (298).

The autosomal dominant mutation of *KCNJ2* causes Andersen–Tawil syndrome (LQT7), having a characteristic triad of episodic flaccid muscle weakness, ventricular arrhythmias, and prolonged QT interval (299) (TABLE 1). Pharmacological approaches to investigate *KCNJ2* loss-of-function mutation revealed that the I_{K1} blocker $BaCl_2$ prolonged the QT interval without causing a major increase in transmural depolarization. EADs and spontaneous torsades de pointes arrhythmias were not observed, nor could they be induced by electrical stimulation. These observations may explain why QT prolongation of the Andersen–Tawil syndrome was found to be relatively benign in clinical settings (300).

The upregulation of $K_{ir}2.1$ was observed in atrial fibrillation, where it may contribute to APD shortening (205). In contrast, $K_{ir}2.1$ downregulation was reported in HF, leading to APD prolongation and facilitating delayed afterdepolarization (DAD) formation (157). Sections 7.1, 7.2, 7.3, and 7.5 provide more detailed information regarding the relevance of altered I_{K1} function and expression in several diseases.

3.6. Ultrarapid Delayed Rectifier Current

The channel carrying the ultrarapid delayed-rectifying potassium current (I_{Kur}) was first cloned from human ventricles (301) but is markedly more expressed in atria (302). At first, it was considered to be a sustained component of I_{to} (303)—“ $I_{to,sus}$.” However, this current is carried by a distinct channel consisting of one $K_v1.5$ α -subunit, encoded by the *KCNA5* gene, and $K_v\beta1.2$ and 1.3 accessory subunits (304, 305).

I_{Kur} is activated rapidly upon depolarization at membrane potentials more positive than 0 mV, with an activation τ of 13 ms at 0 mV potential (302). I_{Kur} inactivates slowly at depolarized potentials, with a double-exponential τ (609 ms and 5,563 ms, respectively, at +40 mV voltage) (306), and its inactivation can be enhanced by sympathetic stimulation (307). This current is thought to operate during phases 1–3 of the action potential of atrial cardiomyocytes and Purkinje fibers but not in ventricular muscle. However, this was challenged by the group of Carnes (308), who measured I_{Kur} as a 4-AP-sensitive current in dog ventricular myocytes. In these dog ventricular myocytes, 50 μ M 4-AP also lengthened APD. These findings, however, need to be confirmed by other investigations. In connection with this, similar mRNA expression levels were measured in ventricles and in Purkinje fibers, but one order of magnitude smaller than in atria (85). Since mRNA measurements from cardiac samples may be contaminated by coronary vessel neuronal tissue and also mRNA from fibroblasts, whether

I_{Kur} exists and/or operates in ventricular muscle is still not fully clarified (252). This question is particularly important because the impact of I_{Kur} on the cardiac repolarization seems complex (309). After the discovery of I_{Kur} , it was thought that selective I_{Kur} inhibitors would have a particular advantage in the treatment of atrial fibrillation, by lengthening APD and ERP in the atria but not in the ventricles. Despite promising animal experiments, these expectations have not been fulfilled, since clinical studies did not result in convincing outcomes with newly developed I_{Kur} blockers (FIGURE 6), e.g., XEN-D0101 and XEN-D0103 (310, 311). Inhibition of I_{Kur} by XEN-D0101 and XEN-D0103 (310) moderately but significantly increased APD in atrial preparations from patients with atrial fibrillation and remodeling, whereas no significant changes were observed in preparations from patients with sinus rhythm (309). These experiments also showed that I_{Kur} inhibition shifts the atrial plateau phase toward the positive direction, thus potentially affecting activation, inactivation, or deactivation of other plateau currents, most notably I_{Kr} . Thereby, I_{Kur} inhibition may produce variable effects of APD and repolarization depending on tissue and experimental conditions (154). This could have important implications if I_{Kur} is actually present in the ventricles, where repolarization reserve would be decreased by I_{Kur} inhibition, with a consequent increase in proarrhythmic risk. I_{Kur} is under adrenergic control: α_1 -receptor stimulation reduces and β_1 -receptor stimulation increases this current in atrial myocytes (306).

3.7. Calcium-Activated K^+ Current

This current is conducted by small-conductance calcium-activated potassium channels (SK2 or $K_{Ca2.1-2}$ and 3), which constitutively bind calmodulin and are encoded by *KCNN1*, *KCNN2*, and *KCNN3* genes (5). The question of whether a calcium-activated K^+ current exists in cardiac tissue and what impact it could have on the action potential was raised long ago (312). Although >35 yr have passed since then, and its existence is now well established in various species and tissues (313), its physiological and pathophysiological roles in cardiac muscle are still not fully elucidated. Most evidence suggests that this current plays a role in the atria (5, 314), and it is also implicated in diseases such as atrial fibrillation and heart failure (5, 315–317). A recent study in rat ventricle showed that SK2 channels are upregulated in HF and also enhanced by PKA phosphorylation (318). In atrial myocytes isolated from patients with AF, SK2 current was increased by enhanced activation of CaMKII (319). The calcium-activated K^+ current is activated in a voltage-independent manner or in response to intracellular Ca^{2+} concentration increase, with a half-maximal activation of 300 nM $[Ca^{2+}]_i$ (320). Despite SK2 channel

expression, this current was not detected, nor was APD lengthened by apamin, the most established inhibitor of this channel, in rat, dog, rabbit, and human undiseased ventricular muscle, thus bringing into question its role in physiological conditions (321). However, other studies have reported an important role for SK2 channels in the human atria.

Most of the evidence regarding the highly apamin-sensitive SK2 current originates from experiments carried out in mice, rats, or rabbits (313, 315, 322, 323). In these species, atrial cellular electrophysiology is not well explored and may differ from dogs or humans. In addition, a marked chloride current was described in rabbit atria that was not found in dog or human atria (324). Furthermore, some of the evidence comes from drug studies performed with NS8593, a putative selective inhibitor of SK2 channels (5), whose effects on all important ionic currents in native cardiac cells have not been tested. Therefore, further investigations are needed for a better understanding of the exact role of SK2 current in cardiac physiology and pathophysiology, which is currently a very interesting and important issue.

3.8. Ligand-Gated Ion Channels

3.8.1. ATP-sensitive potassium channels.

ATP-sensitive potassium channels, carrying the $I_{K_{ATP}}$ current, were first identified in cardiac sarcolemmal membrane by Noma in 1983 (325). K_{ATP} channels were first cloned by Aguilar-Bryan and colleagues (92) and comprise heterooctamers consisting of four inward-rectifying potassium channel pore-forming subunits ($K_{ir6.1}$ or $K_{ir6.2}$, encoded by *KCNJ8* and *KCNJ11* genes, respectively) and four ATP-binding cassette protein sulfonylurea receptors (SUR1 or SUR2, encoded by *ABCC8* and *ABCC9* genes, respectively) (326). The SUR2 has two alternative RNA splice variants, SUR2A and SUR2B; the two polypeptides differ in their COOH terminals (327). Different tissues express K_{ATP} channels with distinctly different subunit composition, thus leading to distinct pharmacological properties of these channels; the myocardial plasma membrane K_{ATP} channel consists of $K_{ir6.2}/SUR2A$ (327). At first glance, their nomenclature might be misleading: these channels are kept closed by physiological intracellular ATP levels in normoxic cardiac tissue, and they activate during metabolic stress, when the ratio of ATP to ADP is decreased, e.g., in myocardial ischemia (328). This makes these channels unique, directly connecting cellular metabolism to membrane excitability. K_{ATP} channels are not regulated by membrane voltage or calcium levels. Indeed, they belong to the inward rectifier (K_{ir}) potassium channel group, with

$I_{K_{ATP}}$ exhibiting weak inward rectification properties on the current-voltage relationship that is regulated by intracellular Mg^{2+} and polyamines (329–331). Activation of sarcolemmal $I_{K_{ATP}}$ during myocardial ischemia heterogeneously shortens the action potential, and may promote reentry (31). Accordingly, several investigations found K_{ATP} activation to be proarrhythmic (332), thus suggesting sarcolemmal $I_{K_{ATP}}$ inhibition for the prevention of myocardial ischemia and ischemia-reperfusion-induced arrhythmias (333–335). In contrast, some studies found no antiarrhythmic effects of K_{ATP} blockers in this setting (336, 337). Furthermore, pharmacological K_{ATP} channel activation was also found to exert antiarrhythmic effects (200, 338, 339) that could be, at least in part, be explained by reduction of monophasic action potential duration heterogeneity (340) and decreased triggered activity in Purkinje fibers upon K_{ATP} opener administration after myocardial infarction (341, 342). It should be also emphasized that K_{ATP} channel activation is very important for prolongation of cell survival during ischemia, since, according to the classical hypothesis, the consequent action potential shortening would reduce contractility by reducing calcium entry into the cardiomyocytes and enhancing Ca^{2+} extrusion via forward-mode NCX activity (343–345). However, cardioprotection following sarcolemmal $I_{K_{ATP}}$ activation in quiescent myocardial cells subjected to hypoxia was also observed (346), suggesting that decreased Ca^{2+} overload via reduced reverse-mode NCX activity during resting membrane hyperpolarization (347) can also contribute to sarcolemmal K_{ATP} -mediated cardioprotection. Therefore, the effects of K_{ATP} channel modulation on ischemia and ischemia-reperfusion-associated cardiac arrhythmias remains controversial.

In addition to the K_{ATP} channels found in the sarcolemma, K_{ATP} channels are also present in mitochondria (348, 349). Evidence suggests that both sarcolemmal and mitochondrial K_{ATP} play cardioprotective roles, albeit via different mechanisms (350). However, because of the lack of truly specific modulators for sarcolemmal and mitochondrial K_{ATP} channels, this remains controversial and further research is needed.

3.8.2. Acetylcholine- and adenosine-activated potassium channels.

It has been known for a long time that acetylcholine shortens APD and has been implicated in atrial fibrillation (351). The ion channel that is directly affected by acetylcholine is called GIRK1/4 or $K_{ir3.1}/K_{ir3.4}$ channel (352, 353), encoded by *KCNJ3* and *KCNJ5* genes, whose α -subunits are closely coupled to muscarinic M_2 - and adenosine A_1 -receptor proteins (354). These channels carry an inwardly

rectifying current, the acetylcholine-activated potassium current ($I_{K_{ACh}}$), and are largely expressed in atrial, SA, and AV nodal cells (355, 356). $I_{K_{ACh}}$ (355, 356) is particularly important in atrial, sinus, and AV nodal cells where they are abundantly expressed. Genes for $K_{ir3.1}$ and $K_{ir3.4}$ are also present in significant amounts in human cardiac Purkinje fibers (85), consistent with the observation that acetylcholine and carbachol shorten APD via $I_{K_{ACh}}$ in atria, SA, and Purkinje fibers (357). However, its influence on repolarization in the ventricles is uncertain (205), and its expression level is relatively low (85). It must be emphasized that increased parasympathetic tone and adenosine can also indirectly decrease $I_{Ca,L}$ amplitude, through the G inhibitory protein decreasing cAMP, thus contributing to shortening of repolarization and shifting the plateau potential toward the negative direction. The $I_{K_{ACh}}$ -induced repolarization shortening is generally considered an important factor in the development of atrial fibrillation (358), and this initiated intensive efforts in the drug industry to develop specific $I_{K_{ACh}}$ inhibitors (359). Cholesterol was also reported to enhance $I_{K_{ACh}}$ (360). The $I_{K_{ACh}}$ current has an important role in modulating the resting or maximal diastolic potential as well, thus hyperpolarizing atrial, SA, and AV nodal tissues and Purkinje fibers. This effect interferes with the pacemaker function, slowing the rate of spontaneous automaticity (361), and it could also slow conduction in the SA and AV nodes, since hyperpolarization can increase the potential difference between the maximum diastolic potential and threshold of activation of $I_{Ca,L}$, which is responsible for depolarization in these tissues.

It has been reported that $I_{K_{ACh}}$ is constitutively active (362) in atrial cells isolated from patients with chronic atrial fibrillation (358) and therefore plays a pivotal role in the shortening of APD or ERP and in the development of atrial fibrillation. Interestingly, however, downregulation of *KCNJ3* gene coded mRNA, $K_{ir3.1}$ channel protein, and $I_{K_{ACh}}$ and upregulation of microRNA (miR)-30d were also observed in atrial tissue obtained from patients with atrial fibrillation (363). In this study, downregulation of $K_{ir3.4}$ protein was also reported (363), thus suggesting a complex, microRNA-regulated ion channel expression in atrial fibrillation that needs further investigation. In addition, after adenosine-induced atrial fibrillation, APD shortened, more so in the right than in the left atrium, and this effect was prevented by inhibition of $I_{K_{ACh}}$ with the selective blocker tertiapin (364). Accordingly, the expressions of both adenosine receptor and $K_{ir3.4}$ GIRK4 channel protein were different between the right and the left atrium (365), thus suggesting a possible role of $I_{K_{ACh}}$ effect heterogeneity in evoking atrial fibrillation.

Recently, it has been reported that an inherited gain-of-function mutation of *KCNJ5* caused familial human sinus node disease. The enhanced activity of GIRK

channels was associated with maintained hyperpolarization of the pacemaker cells that resulted in reduced heart rate (366).

3.9. Chloride Channels

Chloride or anion currents in cardiac muscle were described long ago (367). However, despite intensive and valuable research by some laboratories, relatively little attention has been paid to their possible role in cardiac electrophysiology and arrhythmogenesis (368). One possible explanation is that the functions of chloride channels are diverse (369, 370) and complex and their activation usually needs external triggers like enhanced intracellular cAMP, Ca^{2+} , and swelling or stretch (371). Also the research on Cl^- currents is hindered by the lack of specific blockers, since the established inhibitors of these currents, e.g., DIDS, 9-anthracene (9-AC), tamoxifen, and Cd^{2+} , are not specific. For these reasons, there are uncertainties regarding the degree to which Cl^- channels affect different types of cardiac action potentials. In the basal condition, they carry less current than other well-established transmembrane ion channels. However, in pathological conditions they may play a more important role on arrhythmogenesis than previously thought. Therefore, Cl^- channels deserve more attention, ideally in large-animal or human hearts.

So far, at least four Cl^- channels have been identified convincingly in the heart (369, 370).

3.9.1. Calcium-activated Cl^- channels.

It has been suggested that a current with properties similar to I_{to} may be carried by Ca^{2+} -dependent chloride and potassium currents (372, 373). In this context, it is important to note that the first report of I_{to} in calf Purkinje fiber by Dudel et al. (372) attributed the current to a Cl^- conductance. The kinetics of this Ca^{2+} -dependent I_{to} reflects the kinetics of the calcium transient or rather the changes of intracellular Ca^{2+} in the vicinity of the sarcolemma. This current was also defined earlier as I_{to2} or $I_{\text{to,slow}}$ and could be abolished by depleting the intracellular Ca^{2+} store with caffeine (374) or directly inhibited by DIDS or SITS (375) or by 9-anthracene (9-AC). To avoid confusion, it must be emphasized that this current should be distinguished from the $\text{K}_v1.4$ current, which has also been referred to recently as slow I_{to} because of its slow recovery from inactivation. The physiological and pathophysiological roles of the Ca^{2+} -dependent I_{to} are not well defined but were suggested to play some role in frequency-dependent APD regulation and to secure or shorten repolarization, possibly preventing or diminishing calcium overload in pathological settings

(376). It has been also demonstrated that TMEM16 and Bestrophin-3 are colocalized with $\text{Ca}_v1.2$ in canine and human left ventricular myocytes. In line with this, it was found that activation of calcium-activated Cl^- current ($I_{\text{Cl,Ca}}$) requires Ca^{2+} entry through sarcolemmal $I_{\text{Ca,L}}$, and it is activated by Ca^{2+} release from the SR. Furthermore, $I_{\text{Cl,Ca}}$ exerts an early repolarizing and a late depolarizing component during the action potential, determined by 9-anthracene current in canine ventricular myocytes (377).

Despite the fact that $I_{\text{Cl,Ca}}$ had been discovered a long time ago in the heart, its genetic background was not known for some time and was first attributed to the bestrophin channel protein encoded by the *VMD* gene (378–380), even if later *TMEM16* was reported as an alternative (381–383). The impact of this current on the action potential is different from the other Cl^- currents since it is strongly and dynamically dependent on the intracellular Ca^{2+} concentration (375, 384, 385). It has an important contribution to phase 1, early plateau repolarization, and it also contributes to the repolarization reserve. During Ca^{2+} overload, when spontaneous Ca^{2+} release can happen during diastole, $I_{\text{Cl,Ca}}$ can contribute to the development of DADs by carrying inward current at voltages more negative than the Cl^- equilibrium potential (386). Recently, an anoctamin 1 (*ANO1*)-encoded Ca^{2+} -activated Cl^- channel was identified in the ischemic heart, and its increased density was attributed, at least in part, to the genesis of ischemia-induced arrhythmias (387).

In contrast, in 5-day infarcted canine heart, the I_{to2} current measured from myocytes of the epicardial border zone exerted a significantly smaller peak amplitude, which may contribute to the development of an abnormal action potential (388).

3.9.2. cAMP-dependent cystic fibrosis transmembrane conductance regulator Cl^- channels.

These channels are mostly closed under basal condition, and they carry outwardly rectifying Cl^- current only when intracellular PKA- and PKC-dependent phosphorylation is enhanced. Since the equilibrium potential for Cl^- in normal conditions is between -65 and -40 mV (389–391), they can carry both inward and outward current during the action potential. However, because of its outward rectification, the main effect of the cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- current is to shorten APD and consequently ERP, which in turn may facilitate reentry arrhythmias. Interestingly, it was found that the CFTR Cl^- current abolishes early and late preconditioning and also plays a role in

postconditioning-related cardioprotection (392). It was also reported that intracellular Na^+ modulated the cAMP-dependent regulation of this channel (391).

3.9.3. Swelling- and acidosis-activated Cl^- channels.

In cardiac myocytes, another Cl^- channel was also described, encoded by the *CIC-2* gene and carrying a current that is activated by hyperpolarization more negative than -40 mV, with a relatively slow biexponential time course (393). The current is increased by swelling and acidosis, and it is blocked by 9-AC and Ca^{2+} but not by tamoxifen or DIDS (394). *CIC-2* current, also called $I_{\text{Cl,ir}}$, is strongly rectifying in the inward direction (370, 394, 395), and therefore it plays no or little role in cardiac repolarization. However, it seems to be important in the SA node (396), where it is abundantly expressed, and may contribute to enhanced automaticity during ischemic cell swelling and acidosis.

There are some data regarding a strongly outwardly rectifying acidosis-induced Cl^- current ($I_{\text{Cl,acid}}$), but its molecular entity is unknown. It can be assumed that this current can contribute to the APD shortening in ischemia (397).

Protein tyrosine kinase is one of the initial factors responding to cell swelling, providing the possibility that tyrosine kinase is an important upstream regulator of the swelling-activated Cl^- current ($I_{\text{Cl,swell}}$) (398, 399). Furthermore, angiotensin II is released during stretch, and it is implicated in cardiac remodeling and development of HF, where $I_{\text{Cl,swell}}$ is chronically activated (400, 401). Block of AT_1 receptors prevented activation of $I_{\text{Cl,swell}}$, thus suggesting a potential role of angiotensin II in the activation of the current (402).

3.9.4. Volume-regulated *CIC-3* Cl^- channels.

The channel encoded by the *CIC-3* gene carries a time-independent and robust outwardly rectifying Cl^- current ($I_{\text{Cl,swell}}$) that is small in basal isotonic conditions but is increased by swelling or stretching (369, 370). During ischemia and reperfusion, when swelling of myocytes can occur, $I_{\text{Cl,swell}}$ shortens APD and may enhance dispersion of repolarization between ischemic and nonischemic zones, thus facilitating both atrial and ventricular fibrillation (371, 393). Since the *CIC-3* channels are expressed in atria, ventricles, Purkinje fibers, and SA node cells, they could also play a role in mechanotransduction and in normal pacemaker function, and they may contribute to the development of extrasystoles by promoting membrane depolarization in both the atria and ventricles during stretch (403, 404). *CIC-3* chloride

channels are constitutively active in cardiac hypertrophy and heart failure (370, 371). This may limit APD prolongation, but it may facilitate DADs at elevated diastolic $[\text{Ca}^{2+}]$. In addition, since I_{to} and I_{K1} are downregulated in the failing heart (7), this persistent $I_{\text{Cl,swell}}$ may further change the balance of inward and outward currents toward the inward direction, thus favoring membrane depolarization (405). It was also reported that targeted inactivation of the *CIC-3* gene prevents the cardioprotective effect of the late but not the early phase of preconditioning in mice (405).

3.10. Two-Pore Domain Channels

Two-pore domain K^+ channels ($\text{K}_{2\text{P}}$) are widely expressed in different organs, including the heart, but relatively little is known regarding their function in the myocardium. Except for a few studies, the physiology of these channels has been studied only in mice or rats, but they are abundantly expressed in the human heart as well (406, 407). In general, two-pore domain K^+ channels represent a superfamily of large-conductance K^+ channels, which lack voltage dependence or may exhibit outward rectification (64, 408). They are composed of two α -subunits, each containing four transmembrane segments that form two ion-conducting large-conductance pores (FIGURE 3), and may be associated with several types of accessory subunits (5, 64). These channels are considered important determinants of background K^+ conductance (408). They contribute to the resting or maximal diastolic potential and to the repolarization phase and are regulated by stretch, pH, temperature, and lipids or various signaling messengers (408). In general, the exact roles of the two-pore channels in cardiac electrophysiology and arrhythmogenesis are not well explored and offer challenging targets for further research. Therefore, future intensive research seems worthwhile to clarify the function of these channels in larger mammals and humans, including their potential role in arrhythmogenesis.

3.10.1. TWIK-1 channels.

The “two-pore” or “Tandem of pore domains in a weak inward-rectifying K^+ channel 1” (TWIK-1) channel, encoded by the *KCNK1* gene, was first described in 1996 (407). They are expressed in the heart, are activated by mechanical stretch, intracellular acidification (409), and polyunsaturated fatty acids, and facilitate repolarization and membrane hyperpolarization (5). Recently, it has been reported that TWIK-1 channels can change selectivity from K^+ to Na^+ under extracellular acidic conditions and low K^+ concentration

(410), and this phenomenon is responsible for the paradoxical depolarization contributing to enhanced arrhythmic activity in hypokalemia (411).

3.10.2. TASK-1 ($K_{2P3.1}$) and TASK-3 (K_{2P9}) channels.

The “TWIK-related acid-sensitive K^+ ” (TASK) channels, encoded by the *KCNK3* and *KCNK9* genes, respectively, are voltage-independent channels highly sensitive to extracellular pH, and TASK-1 channels can be selectively inhibited by A293 (5, 64, 412). TASK-1 channels can contribute to APD shortening in ischemia because of their inhibition by extracellular acidosis (412). In addition, they were shown to be upregulated in the atria of patients with chronic atrial fibrillation and preserved cardiac function (413), whereas a downregulation was recently observed in the atria of patients with atrial fibrillation and reduced cardiac function (414, 415), associated with atrial APD shortening (412) and prolongation, respectively. In human atria, TASK-1 channels can form heterodimers with TASK-3 channels (*KCNK9*) that can be regulated by stress and thus contribute to the pathogenesis of chronic atrial fibrillation (416, 417). Interestingly, a gain-of-function mutation in the TASK-4 (*KCNK17*) channel, which is sensitive to pH in the alkaline direction, was reported recently (418), linked to a severe conduction disorder and suggesting the role of the TASK-4 channel in both repolarization and membrane hyperpolarization-related conduction changes.

3.10.3. TREK-1 ($K_{2P2.1}$) channels.

The “TWIK-related K^+ -channel” (TREK-1) represents another two-pore K^+ channel entity that is widely and abundantly expressed in various cardiac tissues (5, 419, 420). TREK-1 channels are particularly important since they carry the outwardly rectifying K^+ current activated by stretch (420), the so-called stretch-activated cation current (SAC), temperature, or polyunsaturated fatty acids, the latter also called arachidonic acid-sensitive current (I_{KAA}). TREK-1-mediated SAC can shorten repolarization, by carrying outward current during the whole duration of the action potential, and hyperpolarize the membrane, thus in turn affecting spontaneous frequency and impulse conduction. This current seems to play a larger role in the atria and SA node than in the ventricles. However, a pathophysiological effect known as “commotio cordis,” describing the accidental chest hit that can cause sudden cardiac death, is presumably due to the function of TREK-1 channels in the ventricles (420). Interestingly, mutations in the selectivity filter can make the TREK-1 channels permeable to Na^+ , thus causing ventricular tachycardia (421). TREK-1 channels are downregulated in atrial fibrillation and heart failure (422–425). They also mediate cardiac fibrosis and diastolic dysfunction, via activation of c-Jun NH₂-terminal kinase (JNK) in myocytes and fibroblasts (426, 427), thus enhancing the propensity of arrhythmias. Genes (*Popdc 1–3*) were identified encoding the cAMP-binding Popeye protein, which associates with TREK-1 channels,

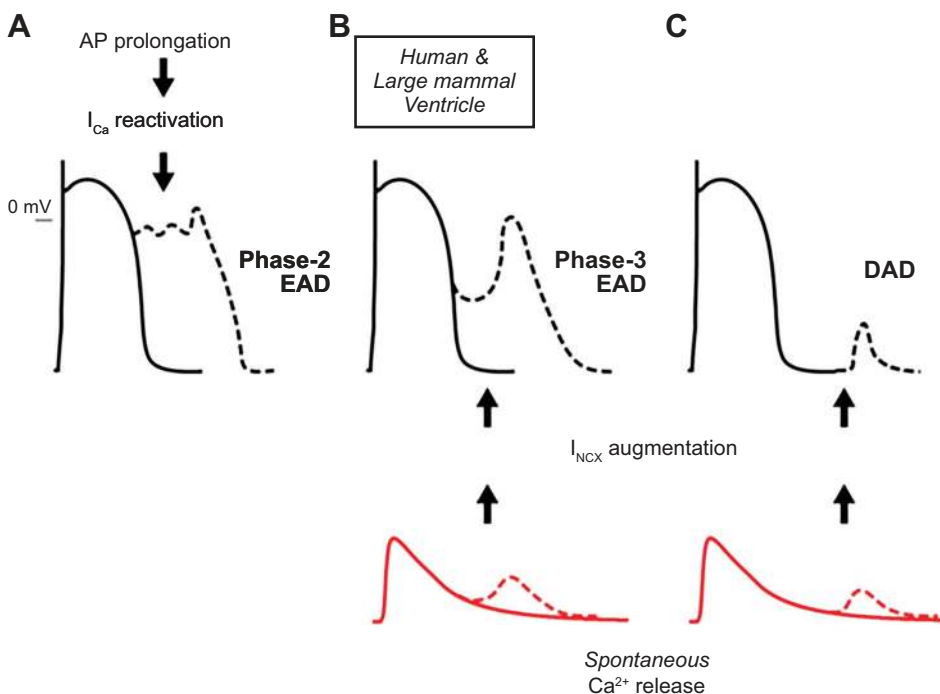


FIGURE 10. Mechanisms of afterdepolarization formation in cardiomyocytes. In ventricular myocytes from large mammals, phase 2 early afterdepolarizations (EADs) are associated with L-type Ca^{2+} current ($I_{Ca,L}$) recovery from inactivation and reactivation during prolonged action potentials (APs) (A). Spontaneous sarcoplasmic reticulum Ca^{2+} release, which increases Ca^{2+} extrusion via Na^+/Ca^{2+} exchange (inward current) (I_{NCX}), can lead to phase 3 EADs (B) or delayed afterdepolarizations (DADs) (C) when occurring during or after the termination of repolarization, respectively. (Reproduced from Ref. 434 with permission.)

modifying their function. Accordingly, the absence of *Popdc 1–2* genes should reduce TREK-1 current, increasing sinus node activity; however, the opposite has been observed experimentally in mouse mutants (242, 428), suggesting the presence of yet unidentified interaction partners for Popeye proteins. Recently, it was proposed that TREK-1 channels could also play a role in establishing the two levels of resting potential (429), a phenomenon that had been described long ago in ventricular and Purkinje fibers (430, 431).

3.10.4. Two levels of resting potential.

Because of the N-shaped steady-state current-voltage relationship of the Purkinje (431, 432) and ventricular (433) cells, two stable levels of resting membrane potentials can develop in these cells. The conductance of potassium channels at 4 mM extracellular $[K^+]$ near the equilibrium potential for K^+ is ~ 100 times greater than that of the Na^+ and Ca^{2+} background channels; therefore it determines the resting potential to be around -90 mV. When the conductance of potassium channels decreases because of I_{K1} inward rectification (FIGURE 9) and/or hypokalemia, the conductance ratio of K^+ and Na^+/Ca^{2+} channels can dramatically decrease, which results in a second stable, albeit lower, potential in the range of -50 to -25 mV depending on extracellular $[K^+]$ or the actual strength of the background Na^+ and Ca^{2+} currents (431–433). This second stable potential has an important role in the genesis of the arrhythmogenic triggered spontaneous automaticity like phase 2 or 3 early afterdepolarizations (FIGURE 10).

3.11. Transmembrane Ion Transporters

Transmembrane ion transporters, which exchange cations across the sarcolemma, are essential to maintain the uneven ion distribution between the extra- and intracellular space. These ion pumps influence cardiac cellular electrophysiology indirectly, by changing various intracellular concentrations (282), most importantly Ca^{2+} , which activates and regulates several other transmembrane ionic currents. In addition, some transmembrane ion transporters are electrogenic, i.e., they exchange charges unevenly, thereby carrying inward or outward transmembrane ion currents, which can influence the action potential repolarization and maximal diastolic or resting potential.

3.11.1. The Na^+-K^+ ATPase/pump.

The primary role of the Na^+-K^+ pump (NKA) is to remove from the intracellular space the Na^+ that

enters during the action potential (36). The pump exchanges 3 Na^+ for 2 K^+ and thereby carries an outward current ($I_{Na/Kpump}$) (282). The size of the generated current ranges between 0.34 and 0.68 pA/pF (37), which can result in RMP changes of 8–9 mV at near-physiological conditions (35, 38), even though its effect is often overlooked. It plays an important role in ionic homeostasis and also in cardiac repolarization (435). The $I_{Na/Kpump}$ shortens repolarization in simulations (436), contributes to the resting potential, and, if its activity is enhanced by elevated extracellular $[K^+]$, intracellular Na^+ concentration ($[Na^+]$), cAMP, or high firing rate (437), can even hyperpolarize the cell (438). The Na^+-K^+ pump needs energy to work, since it pumps out Na^+ against its electrochemical gradient. The source of this energy comes from intracellular ATP, through the function of the Na^+-K^+ -ATPase, which is part of the pump (438). So far, two α -subunits have been identified for NKA: α_1 and α_2 (439, 440). The α_1 is evenly distributed in the sarcolemma (441), and it regulates intracellular Na^+ in the bulk of the cytoplasm. The α_2 is mostly expressed in the dyadic cleft (440, 442, 443) and therefore may have a special role in controlling, via interaction with the NCX, the Ca^{2+} released from the sarcoplasmic reticulum (440). The fact that the α_1 -subunits of the Na^+-K^+ pump are evenly distributed in the sarcolemma and carry $>80\%$ of the $I_{Na/Kpump}$ (440, 444) raises the possibility to develop drugs that selectively modulate the Na^+-K^+ pump α_1 - and α_2 -subunits (440). As well as being regulated by intracellular Na^+ concentration (445), Na^+-K^+ pump activity is controlled by the phosphorylation of FXYD protein phospholemman (PLM) (446). Dephosphorylated PLM exerts a tonic inhibition of Na^+-K^+ pump, and its phosphorylation would relieve this inhibition. Stimulation of the β -receptor increased the pump activity (447), and α -receptor activation enhanced the Na^+-K^+ pump in canine Purkinje fibers (448). It was further reported that insulin flattened the pump current (I_p)-voltage (V) curve of the pump, depending on the patch pipette $[Na^+]$ and voltage (449). The β -subunit is also essential for pump function, providing a stabilization role for the α -subunit. The γ -subunit seems to contribute in regulation of the sodium pump activity (450, 451).

The cardiac glycosides (such as ouabain) are specific inhibitors of the Na^+-K^+ pump (452). Application of 1 μM ouabain increases the AP duration at 90% repolarization (APD_{90}) by 17% and 10 μM by 21%, also increasing the AP plateau (453).

The Na^+-K^+ pump is a key player in the cellular mechanism of ischemia-reperfusion injury. In myocardial ischemia, reduced ATP levels cause a decline in activity

for the $\text{Na}^+\text{-K}^+$ pump. The suppressed function of the pump leads to elevated intracellular Na^+ level, which activates reverse mode of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX), thus providing enhanced Ca^{2+} entry and Ca^{2+} overload (4).

3.11.2. The $\text{Na}^+/\text{Ca}^{2+}$ exchanger.

The NCX is a member of a large Ca^{2+} /cation antiporter superfamily (454). The mammalian tissues express three NCX isoforms, NCX1–NCX3, encoded by the genes *SLC8A1*–*SLC8A3*, respectively (455–457). Alternative splicing of the primary nuclear *SLC8A1* transcript generates at least 17 NCX1 proteins (454), and the NCX1.1 splice variant represents the cardiac isoform of the NCX (458). The NCX1.1 comprises 10 transmembrane segments, where two groups of five transmembrane segments are separated by an intracellular loop (459). This loop contains the exchanger inhibitory peptide (XIP) region that plays a key role in NCX inactivation by increased intracellular $[\text{Na}^+]_i$ (460, 461). The cytoplasmic loop also contains two calcium-binding domains that are responsible for Ca^{2+} regulation of the NCX (462). The main function of the NCX is to control calcium flux through the plasma membrane, and it transports 3 Na^+ for 1 Ca^{2+} , using the driving force of the Na^+ gradient provided by the NKA as discussed previously (458, 463–465). The stoichiometry makes NCX electrogenic (466), with one net positive charge moving either into the cell (“forward mode) or out of the cell (“reverse mode”), eliciting inward or outward transmembrane current (I_{NCX}), accordingly. The magnitude and direction of ion transport and generated transmembrane current therefore depend on the membrane potential as well as the transmembrane concentration gradients of Na^+ and Ca^{2+} , thereby dynamically changing during the action potential (467). During the early phases of the action potential when transmembrane voltage is positive and intracellular Ca^{2+} is low, Ca^{2+} enters the cell by reverse NCX, generating outward current. Later on, when $[\text{Ca}^{2+}]_i$ is increased, Na^+ enters and Ca^{2+} leaves the cell, generating an inward current (468). This function results in complex changes on the cardiac action potential (467) and arrhythmogenicity depending on heart rate, possible Ca^{2+} overload, or NCX expression levels. It was reported that a substantial degree of selective NCX inhibition did not change the shape of the action potential waveform in normal physiological settings in dog ventricular papillary muscle (469, 470) and in human right atrial preparations (471). However, when NCX forward mode was experimentally enhanced in dogs, selective NCX inhibition by 1 μM ORM-10962 shifted the plateau voltage toward negative values (469). On the contrary, when reverse NCX mode was experimentally

augmented, 1 μM ORM-10962 moderately lengthened the action potential (469). It is generally considered that NCX is the major, but not the only (472, 473), source of Ca^{2+} removal from the cell during the later phase of the action potential and diastole, carrying an inward current that can contribute to both EADs and DADs (FIGURE 10). Indeed, it was demonstrated that inhibition of NCX abolishes both EAD and DAD development (470, 474–476) and also arrhythmias caused by enhanced dispersion of repolarization (477) or by ouabain application (469).

Some studies suggest that NCX proteins are relatively concentrated in the dyadic clefts, where the SR-ryanodine Ca^{2+} release site faces the sarcolemma (478–480), but another study (481) provided different results, and thus this issue is still unresolved (440, 463). Na^+ entering the cell can increase the intracellular Na^+ concentration in the small volume of the dyadic clefts, thereby increasing Ca^{2+} entry into the cell on reverse-mode NCX (470, 482). This may increase Ca^{2+} -induced Ca^{2+} release from the SR. It is important to note that Ca^{2+} concentration changes in the clefts and close to the sarcolemma can be orders of magnitude higher than in the bulk of the cytosol (483), which is what is measured routinely with fluorescent Ca^{2+} indicators. Therefore, experiments can severely underestimate the electrophysiological role of NCX in cardiac myocytes. Further methodological improvements are necessary to determine Ca^{2+} concentrations most accurately in the dyads and clefts in order to better define and understand the electrophysiological role of NCX in arrhythmogenesis.

Sorcin is a penta EF-hand protein that interacts with intracellular target proteins after Ca^{2+} binding. It has been reported that NCX1 could be an important target of sorcin: downregulation of sorcin decreases NCX activity, but a higher level of sorcin increases it (484). It was also described that insulin is able to increase the NCX activity via interaction with the 562–670 f-loop domain (485). Furthermore, the wild-type NCX1.1 associates with the F-actin cytoskeleton, probably through interactions involving the central hydrophilic domain of the NCX, and this association interferes with allosteric Ca^{2+} activation (486). Phosphatidylinositol 4,5-bisphosphate (PIP_2) plays an essential role in NCX regulation, since PIP_2 increases reverse-mode NCX1 activity, causing a net increase in Ca^{2+} influx (1133, 1134). Long-chain acyl-CoA esters, found to be elevated in cardiac ischemia (487), hypertrophy (488), and failure (489), have been shown to be endogenous activators of reverse-mode NCX activity by interacting directly with the XIP sequence, and thus linking altered fat metabolism to NCX function and NCX-mediated calcium overload in the myocardium, in

pathological conditions (490). Importantly, protons are powerful inhibitors of NCX1.1 forward-mode activity, further emphasizing the role of NCX1.1 as a key contributor to pathologically altered Ca^{2+} homeostasis and arrhythmia generation during cardiac intracellular acidosis, including myocardial ischemia (491, 492).

The effects of genetic mutations influencing NCX function are poorly understood. However, a genetic mutation in NCX1 was demonstrated to cause cardiac fibrillation in a zebrafish model (493).

3.11.3. The Na^+/H^+ exchanger.

The Na^+/H^+ exchanger (NHE) was first described in rat intestinal and kidney tissue (494). Since then, nine NHE isoforms have been identified (NHE1 to NHE9, encoded by the genes *SLC9A1* to *SLC9A9*, respectively) (495, 496), and in the plasma membrane of mammalian myocardial cells NHE1 is the primary isoform (497). The NHE1 consists of 12 transmembrane segments, with the NH_2 terminal (~500 residues) catalyzing ion transport and interacting with pharmacological NHE inhibitors and the COOH terminal (~300 residues) responsible for regulation of the exchanger by calmodulin, PIP_2 , and calcineurin B homologous proteins (498–504). The NHE1 can be found as a homodimer in the plasma membrane (505). The NHE1 dimer exchanges 2 extracellular Na^+ for 2 intracellular H^+ in one cycle (506), and it is an important regulator of intracellular pH

(507) and cell volume (508). The function of NHE is electrically neutral; therefore, it does not directly affect the AP and arrhythmogenesis in normal conditions. However, it has been shown to play important pathophysiological roles by indirectly changing intracellular Na^+ concentration and pH (509, 510), both affecting several ion channels and transporters. The role of NHE is considered significant in arrhythmogenesis in pathological settings, including myocardial ischemia-reperfusion, heart failure, or diabetes, when intracellular pH or Na^+ deviates from physiological levels (496, 511–514).

4. TISSUE-SPECIFIC ACTION POTENTIALS

4.1. Sinoatrial Node and Pacemaker Function

The sinoatrial node (SAN) is located in the upper part of the right atrium, and it has a special role in the heart, serving as the natural pacemaker. SAN cells have a relatively low maximal diastolic potential (less than -60 mV), that, after the termination of repolarization, gradually becomes less negative during the so-called spontaneous diastolic depolarization—until it reaches the potential range of L-type Ca^{2+} channel activation, thereby generating a new action potential. The exact nature of the pacemaker function in the SAN is still under debate (515–519). Originally, it was thought that the slow diastolic depolarization was

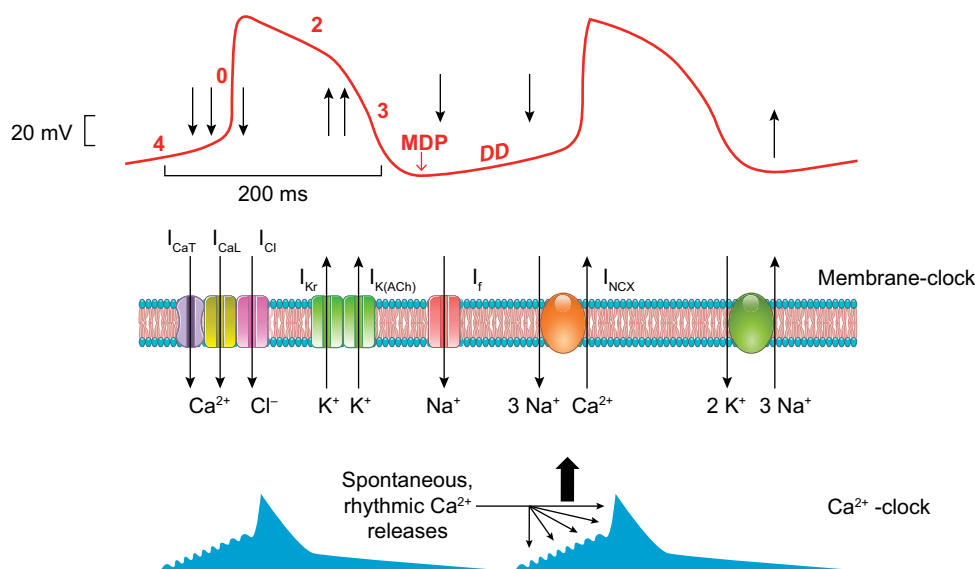


FIGURE 11. Hypothetical mechanism for sinus node pacemaking. The figure illustrates a typical sinus node action potential (red trace) and the timing of the membrane and Ca^{2+} clock components. Upon phase 0, the T ($I_{\text{Ca,T}}$)- and L ($I_{\text{Ca,L}}$)-type Ca^{2+} channels (and presumably the Cl^- channels, I_{Cl}) open, providing inward current (downward arrows), and depolarize the membrane. During repolarization (phase 3) the opening of the delayed rectifier (I_{Kr}) and the acetylcholine-dependent ($I_{\text{K(ACh)}}$) K^+ currents (upward arrows) repolarizes the membrane to reach the maximal diastolic potential (MDP). Upon diastolic depolarization (DD), the cAMP-dependent “funny current” (I_{f}) slowly depolarizes the membrane in close cooperation with the sodium-calcium exchanger (I_{NCX}) that is governed by spontaneous, rhythmic Ca^{2+} oscillations from the sarcoplasmic reticulum.

due to a hyperpolarization-activated inward current. This current was first described in cardiac Purkinje fibers and was thought to be carried by Na^+ , based on its dependence on extracellular $[\text{Na}^+]$ (520). Later on, other studies suggested that the slow diastolic depolarization was the result of a decaying K^+ current called I_{K2} (521, 522). These data were subsequently reinterpreted in terms of ionic currents resulting from extracellular accumulation of K^+ , and a hyperpolarization-activated inward current, called “funny current” (I_f), carried by both Na^+ and K^+ , was described by Di Francesco (524) and others (523, 525). Despite the fact that other currents, such as I_{Kr} , T-type I_{Ca} and NCX, were also suggested to play a role in the SAN pacemaker activity (526–529), for more than two decades since its discovery the major mechanism underlying the pacemaker function was generally considered to be I_f . However, in an early study of Noma, Morad, and Irisawa (530), the significance of I_f in the SAN pacemaker function was questioned. These authors showed that cesium, an inhibitor of I_f , did not influence the SAN spontaneous frequency and did not eliminate the epinephrine-induced increase in SAN frequency. The dominant role of I_f in SAN pacemaker function was later also challenged by studies showing that a cycling spontaneous release of Ca^{2+} happens during diastole, and this can cause spontaneous depolarization by activating forward NCX as an alternative mechanism for the pacemaker function (“calcium clock hypothesis”) (203, 531–534). This controversy seems to be settled by the “coupled clock hypothesis” (FIGURE 11), suggesting an important role for both the “calcium clock” and the “membrane clock” (I_f) (528, 535). Also, in a recent study, Morad and Zhang (517) demonstrated and pointed out that I_f was very small and very slowly activating at the range of maximal diastolic potential of the SAN cells (–60 mV), therefore not enough to generate a significant amount of pacemaker current. These authors suggested that expression and function of inward I_f in SAN cells can counterbalance the electrotonic interaction of the more negative resting potential of the surrounding atrial cells. According to this suggested function, I_f is important since it insulates SAN cells from the hyperpolarizing influence of the atria, thus allowing a proper SAN function. Consistent with this speculation, Boyett et al. (536) found higher HCN (I_f) expression in peripheral rabbit SAN tissue than in the central core.

A recent study in human induced pluripotent stem cell (hiPSC)-derived myocytes suggested that mitochondria could also play a role in the spontaneous activity, setting the rhythm of the “calcium clock” by taking up and releasing Ca^{2+} from and to the cytosol (517). However, other

studies suggested that mitochondrial Ca^{2+} transient decay is slow, and that their Ca^{2+} efflux is relatively small during one cardiac cycle (463), thus raising questions about a significant role of mitochondrial Ca^{2+} release on SAN frequency. Further studies in adult SAN cells are necessary to confirm the possible role of mitochondria in pacemaking.

In general, SAN frequency can be slowed down by inhibiting I_f , NCX, $I_{Ca,L}$, or I_{Kr} in feline, rabbit, and porcine SAN myocytes (537–540). Inhibition of I_f and NCX decreases the slope of diastolic depolarization, while inhibition of $I_{Ca,L}$ would shift the threshold potential toward more positive values, and thereby the cycle length is increased in all cases. Inhibiting I_{Kr} prolongs repolarization of SAN cells and lengthens their spontaneous cycle lengths. It has to be considered, however, that loss-of-function mutation of I_f results in sinus bradycardia, arguing for some role of I_f in SAN pacemaking (541).

SAN frequency can also be affected by intracellular cAMP levels. Elevation of intracellular cAMP increases I_f and shifts its activation to more negative potentials (542), which in turn enhances I_{Ca} and intracellular Ca^{2+} , further favoring the increase of SAN frequency. Vagal stimulation has an opposite effect on intracellular cAMP and SAN frequency. Data from SAN cells isolated from Girk4 ($\text{K}_{ir3.4}$)-knockout mice lacking $I_{K,ACh}$ suggest that it may also activate $I_{K,ACh}$, which can cause hyperpolarization and may also contribute to SAN bradycardia (543).

SAN cells lack cardiac type $\text{Na}_v1.5$ fast Na^+ channels, and therefore their depolarization is caused by $I_{Ca,L}$ (544). Recently, neuronal $\text{Na}_v1.6$ Na^+ channels were reported in SAN cells (90, 545), but their role in SAN function is not well understood (529). The SAN action potential does not show a distinct plateau phase with relatively weak I_{K1} current.

Experimental evidence obtained in spontaneously beating guinea pig sinoatrial cells suggests that I_f function decreases SAN frequency variability, which is the intrinsic behavior of the calcium clock function (546).

Elucidating the exact mechanisms underlying pacemaker function and its regulation still remains an important task for the future, since it provides the regular heartbeat but it can also act as a possible trigger for serious atrial and ventricular arrhythmias (547, 548).

4.2. Atrial Action Potential

Large species-dependent variations make it difficult to describe the general shape of cardiac action potentials, including atrial action potentials (FIGURE 12 and FIGURE 13). There is also significant diversity within the same heart (549), at least in humans (3, 550), and this results in a relatively large dispersion of repolarization, which favors the development of atrial fibrillation.

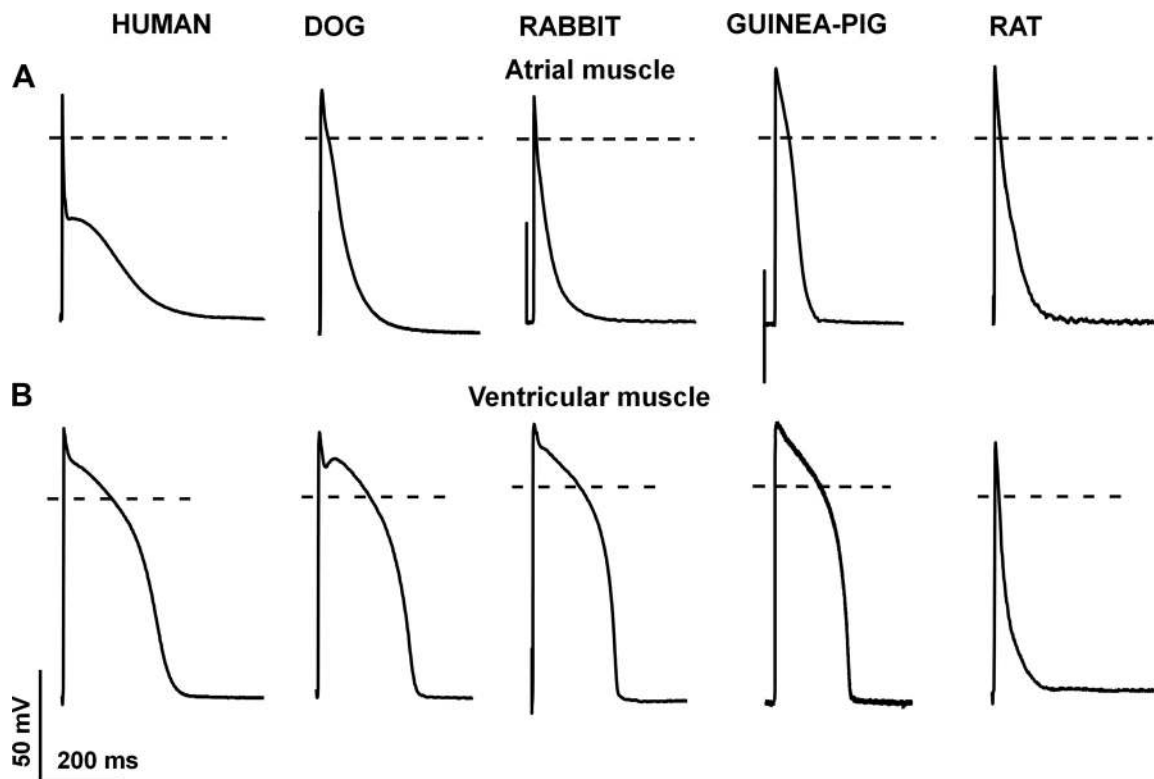


FIGURE 12. Species-dependent differences in atrial (A) and ventricular (B) action potential configuration. Original action potential recordings at 1 Hz stimulating frequency from human, dog, rabbit, guinea pig, and rat ventricular muscle preparations recorded by the conventional microelectrode technique. Unpublished data from our laboratory at the Department of Pharmacology and Pharmacotherapy, University of Szeged.

In most species, the atrial action potential lacks a long and stable plateau phase. In human atria, most of the atrial action potential recordings show a plateau phase, but at a more negative voltage range (-10 to -30 mV) than observed in the ventricle. This is due to the function of the abundantly expressed I_{to} and I_{Kur} potassium currents (FIGURE 6). I_{to} in the atria has slower inactivation kinetics than in the ventricles, having a robust slowly deactivating component ($\tau = 91$ ms at -20 mV), with slower recovery (551) from inactivation ($\tau = 125$ ms) than the ventricular one. Therefore, frequency-dependent changes of APD and restitution are different in atrium and ventricle. In the atria I_{Kur} is large (85) and contributes to repolarization, in contrast with the ventricle, where it is absent or very weakly expressed (85). Therefore, I_{Kur} inhibition would be expected to prolong the AP. However, inhibition of I_{Kur} shortens repolarization by shifting the plateau voltage to the positive voltage range (309), thus changing the activation and deactivation/inactivation of other plateau currents, such as I_{Kr} , I_{Ks} , I_{Ca} , and I_{NaLate} . I_{Kur} inhibition has also been shown to slightly prolong human atrial APD in tissue obtained from chronic AF patients (309, 552). However, in this case, phase 1 and 2 repolarization were delayed and shifted to positive potentials, because of electrophysiological remodeling, thus allowing for a larger I_{Kur} contribution

compared with normal conditions. It is interesting that, in rabbit (unlike in human) atrial muscle, sustained Cl^- current was reported after I_{to} inactivation (324, 553). This should be taken into consideration when drugs are studied in rabbit atrial preparations, and it highlights the importance of species-dependent electrophysiological differences. A distinct, cellular swelling-induced Cl^- current has also been described in human atrial myocytes (554), which is also modulated by PKA-independent, cAMP-mediated β -adrenoceptor signaling (555). The existence and potential role of $Na_v1.8$ channels in I_{NaLate} in the atria represents an interesting issue; however, it is still the subject of debate (556) and requires further studies. L-type and T-type I_{Ca} have similar properties in atria and ventricle (557). I_{K1} current density is relatively small in the atria, especially in the voltage range between -80 and 0 mV. This is consistent with the finding of lower $K_{ir2.1}$ mRNA expression in right atrial compared with right ventricular human tissues (85). Recently, it has also been reported that neurokinin-3 receptor activation induced prolongation of atrial refractoriness, which was attributed to the inhibition of a nonspecific K^+ background current (297). It is difficult to measure I_{Kr} and I_{Ks} in atrial myocytes, most likely because of the cell isolation techniques (252). Regardless of that, I_{Kr} block significantly lengthens atrial repolarization, in both

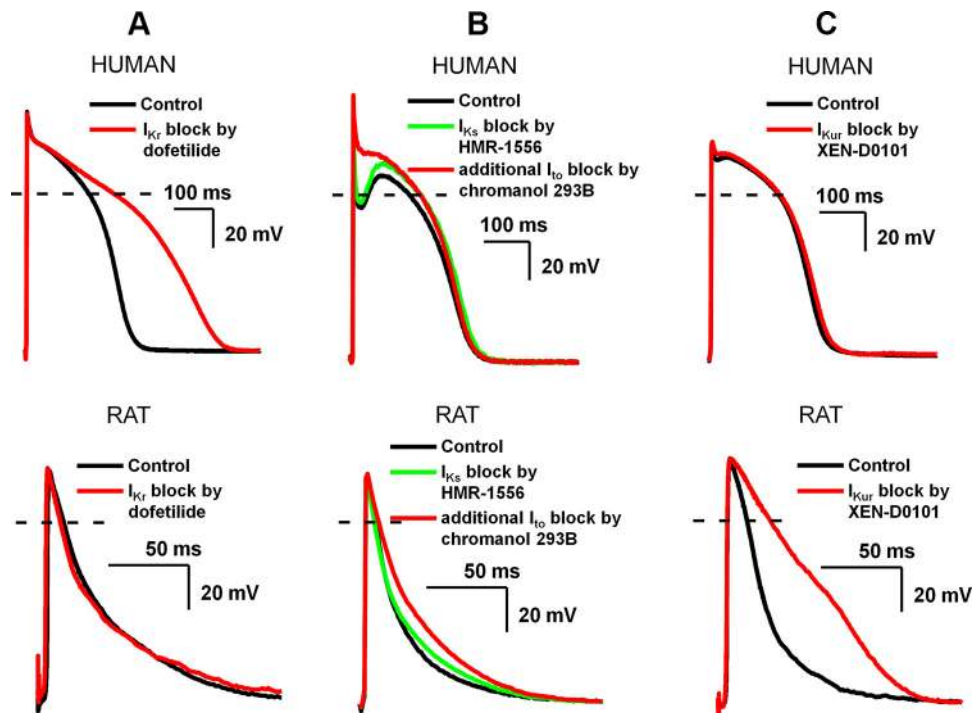


FIGURE 13. Distinctly different effects of slow component of delayed rectifier potassium current (I_{Ks}), transient outward current (I_{to}), and ultrarapid component of delayed rectifier potassium current (I_{Kur}) inhibition on ventricular repolarization in human (*top*) and rat (*bottom*). In these experiments, action potentials were recorded in ventricular papillary muscle with the conventional microelectrode technique at 1 Hz stimulation frequency. Note the extended timescale of the recordings in rat papillary muscle. **A:** rapid component of delayed rectifier potassium current (I_{Kr}) inhibition by 50 nM dofetilide markedly prolonged action potential duration (APD) in human but not rat papillary muscle. **B:** I_{to} block by 100 μ M chromanol 293B in human eliminated the notch and elevated the plateau potential to positive direction without changing the APD; however, the APD was significantly prolonged in rat. Since chromanol 293B fully blocks I_{Ks} in addition to inhibition of I_{to} at 100 μ M, prior I_{Ks} block was elicited by 500 nM HMR-1556 to dissect these effects (140). **C:** I_{Kur} inhibition by 3 μ M XEN-D0101 (310) does not affect APD in human but markedly prolongs APD in rat ventricular papillary muscle (unpublished experiments from the Department of Pharmacology and Pharmacotherapy, University of Szeged).

animal and human studies (558, 559). On the other hand, the role of I_{Ks} in atria is not well explored. Experiments with chromanol 293B on atrial action potential are not conclusive, since this drug inhibits both I_{Ks} and I_{to} (560). It must be emphasized that, in physiological conditions, the atrial plateau voltage is more negative than the activation threshold of I_{Ks} . Therefore, I_{Ks} is not expected to contribute to atrial repolarization. However, it has been reported that in atrial tissue LQT1, MinK, and MiRP levels are similar to those in ventricular tissues (85). On the basis of these results, it can be speculated that, at fast heart rate (enhanced sympathetic tone) and in situations where the atrial plateau is shifted to positive voltage, I_{Ks} may have a role in atrial repolarization. Therefore, its modulation could influence arrhythmogenesis. Indeed, it has been shown that two gain-of-function mutations in *KCNQ1* (S140G and V141M), detected in patients with AF (275, 277), markedly slowed deactivation of I_{Ks} and contributed to the development of AF (561). Unlike in the ventricles, most studies showed the existence and function of small-conductance, apamin-sensitive and calcium-dependent potassium current (SK2) in normal atria, but its significance seems to be far more pronounced in diseased tissue (5, 314, 316, 317,

562). The increased apamin-sensitive SK current was found along with decreased mRNA and protein levels of SK1, SK2, and SK3 channels in human atrial cardiomyocytes isolated from patients with AF (319). However, in the same experiments CaMKII was increased and its inhibition by KN-93 reduced the apamin-sensitive SK currents to a higher degree in myocytes isolated from patients with AF compared with those in sinus rhythm (319), suggesting that SK channels are more sensitive to Ca^{2+} in AF patients and CaMKII modulation may represent a pharmacological target in the management of AF. Neurohormonal modulation of the atria is particularly important. Acetylcholine (358, 563), catecholamines (555, 563), substance P (297), adenosine (564, 565), and serotonin (566) have been reported to influence atrial action potential and its underlying currents. In the atria, $I_{K_{ACh}}$ is robust and even has a small but persistent constitutively active component, which operates without parasympathetic stimulation and seems greatly augmented during chronic AF (358). Accordingly, atrial tissue expresses mRNAs for $K_{ir,3.1}$ and GIRK channels abundantly. Of note, TWIK TASK channels are also relatively abundantly expressed in the atria (85), but their roles in atrial electrophysiology are not well explored yet.

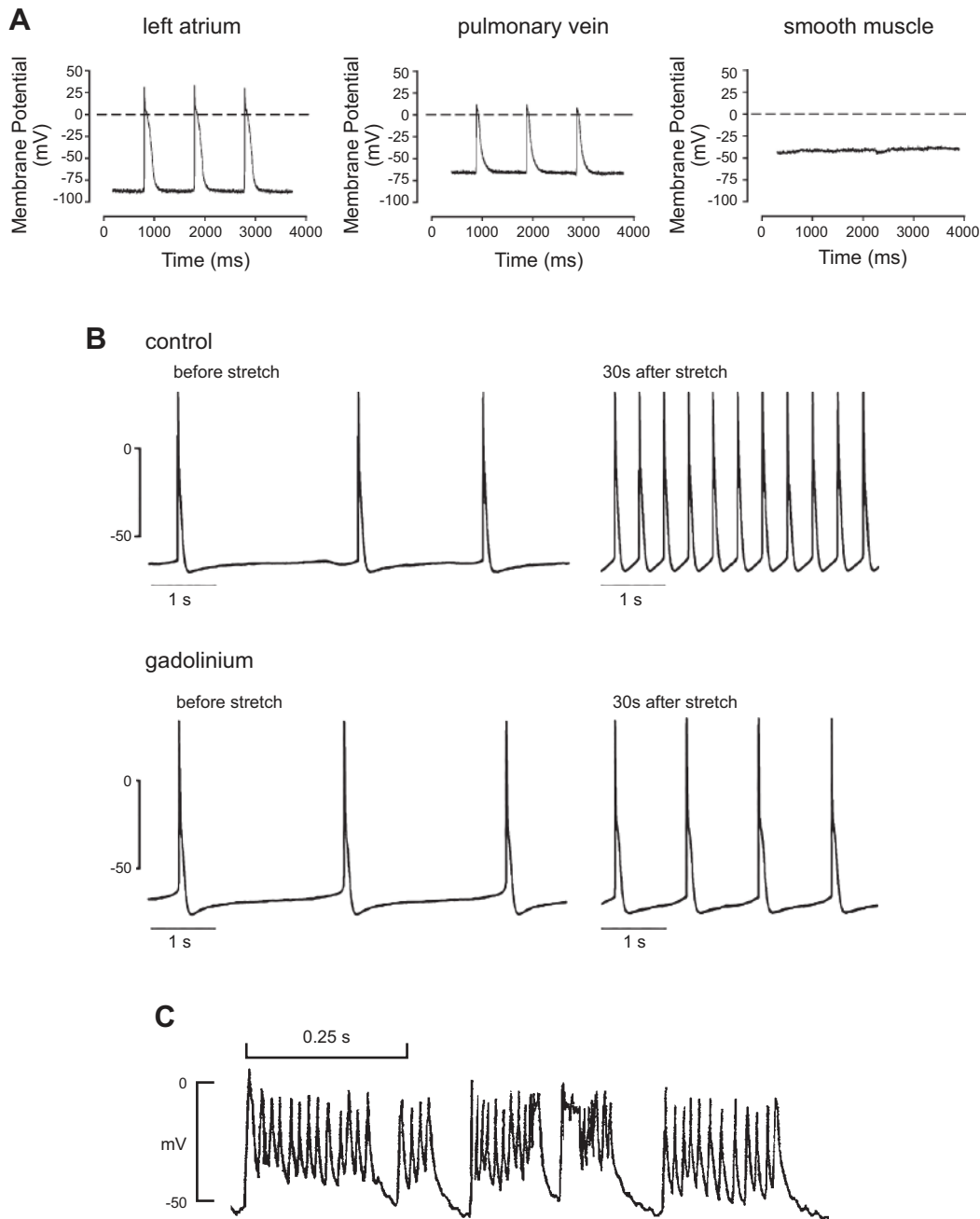


FIGURE 14. Properties of action potentials from left atrial and pulmonary vein myocytes. *A*: recordings of action potentials from the left atrium and pulmonary vein and a transmembrane potential in the smooth muscle cell layer. (Reproduced from Ref. 576 with permission.) *B*: effects of mechanical stretch on the spontaneous electrical activity of the pulmonary vein myocardium. Expanded traces obtained before (*left*) and 30 s after (*right*) the application of mechanical stretch (100 mg) in the absence (*top*) and presence (*bottom*) of gadolinium. (Reproduced from Ref. 577 with permission.) *C*: spontaneous action potential with early after-depolarizations in canine pulmonary veins from dogs subjected to chronic atrial tachypacing. (Reproduced from Ref. 578 with permission.)

4.3. Pulmonary Veins

The spontaneous activity of the pulmonary vein (PV) was described long ago by several investigators (567, 568). Later, Haïssaguerre and colleagues (569, 570) demonstrated that electrical activity in the pulmonary vein sleeves (PVs) in patients has an important role in atrial fibrillation. In the following years, intensive research was carried out both in the clinical and experimental fields

(571, 572), to understand their role (573, 574), the mechanisms, and possible treatment of arrhythmias initiated and maintained by the PVs. It was demonstrated that tissue with myocardial origin is present in the PVs of dogs and guinea pigs, with electrophysiological properties that are similar to but also distinct from the neighboring atrial tissue (568, 575) (FIGURE 14). PVs cells have less negative resting potential and shorter APD than atrial myocytes and also lack a prominent plateau phase

(FIGURE 14). Work on canine PVs found that these cells either do not show spontaneous diastolic depolarization or, if they do, their rate is normally lower than that of SAN cells (576, 579). Stretch can also increase automaticity and induce high-frequency firing in guinea pig PV cells (577) (FIGURE 14). Sympathetic stimulation or diseases like hyperthyroidism (580) increase intracellular $[Ca^{2+}]_i$, causing PVs cells to develop triggered activity (FIGURE 14), and both early (EAD) and delayed (DAD) afterdepolarizations can occur (578) (FIGURE 14). Compared with atrial myocytes, PVs cells have similar I_{CaL} , I_{CaT} , I_{to} , and NCX but lower current density of I_{K1} , I_{Kr} , and I_{Ks} , with inconsistent results available regarding I_{Na} (576, 581). Interestingly, a hyperpolarization-activated inward K^+ current was reported in canine PVs cells, which was highly sensitive to low submicromolar concentration of Ba^{2+} (579). Based on this finding, K_{ir3} subunits were speculated to be involved as the channel background of this current, and it was suggested that it may play a significant role in atrial pathophysiology (579). This current, $I_{K_{ACh}}$, was enhanced in a conscious tachypaced dog AF model, and its inhibition by tertiapin-Q resulted in a marked reduction in the incidence of AF episodes (558).

In rat PV, a voltage-dependent Cl^- current was also reported and suggested to contribute to norepinephrine-induced automaticity in the PVs. (582). PVs electrophysiology is also modulated by a wide variety of drugs that are used in clinical practice including celecoxib, amiodarone, ranolazine, losartan, and enalapril (583–587). Several factors and diseases, e.g., stretch (585), electrolyte disturbances, sex differences, air pollutants (H_2S) (588), thyroid hormone (580), ischemia-reperfusion (589), uremic substances, renal and heart failure, and aging, have been reported to influence the electrophysiology of PVs.

Recently, it was shown that factor Xa inhibitor anticoagulants, which reduce the incidence of AF-related stroke, also decrease the activity of rabbit PV cells, by inhibiting PAR1 and also diminish I_{NaLate} . Based on this, it was speculated that they can modulate the occurrence of atrial fibrillation (590).

Although it is generally accepted that PVs represents an important trigger for arrhythmias, further research in this field is still necessary to fully elucidate the role of PVs in arrhythmogenesis and to develop new effective therapies involving PVs in general (586, 587). Nevertheless, PV isolation by catheter ablation has become an established therapeutic intervention in the management of paroxysmal and persistent AF (591, 592).

4.4. AV Nodal Action Potential and Conduction

Although they have similarities, AV node cells differ from the SAN cells (593–595), with a lower spontaneous

frequency and a more negative maximal diastolic potential (596, 597). The structure of the AV node, like the SAN, includes a large variety of different cell types (598, 599), with different channel expression (600–603). In the rat AV node, high expression levels of HCN4, $Ca_v3.1$, $Ca_v3.2$, $K_v1.5$, $K_{ir3.1}$, and $K_{ir3.4}$ and low expression of $Na_v1.5$ and $K_{ir2.1}$ mRNA were measured compared with those observed in the ventricle (600). In rabbit AV node, no or low expression of $Na_v1.5$, $Ca_v1.2$, $K_v1.4$, KChIP2, and RYR3 and high expression of $Ca_v1.3$ and HCN4 mRNA were reported (601). Like SAN cells, AV nodal cells do not have functioning fast $Na_v1.5$ I_{Na} channels, and therefore their depolarization and impulse conduction depend on the function of I_{CaL} (565, 603). In AV nodal cells, the expression and function of $I_{K_{ACh}}$ is particularly important (604, 605), since their activation via the adenosine 1 or muscarinic receptors (606) hyperpolarizes the AV nodal cells, which slows or blocks impulse conduction in the AV node (607, 608). In addition, adenosine and acetylcholine decrease I_{CaL} via G_i protein signaling pathway, further decreasing the safety of impulse propagation through the AV node. These are the principal cellular mechanisms that make intravenous adenosine so useful in stopping AV nodal reentry tachycardia (604). The T-type Ca^{2+} channel is expressed and is functional in the AV node as in the SAN (607). Indeed, mibefradil, a potent I_{CaT} inhibitor, increased AV nodal conduction time and even elicited second- or third-degree AV block in isolated, blood-perfused dog hearts (607). The slow conduction through the AV node is physiological and provides a time lag for contraction between the atria and the ventricles. AV nodal tissue has diverse and different connexin 40, 43, and 45 distribution compared with other parts of the heart (8), with a complex and diverse structure, containing a dual faster and slower impulse conduction pathway (594, 603, 609). This latter can provide the basis of fixed-rate supraventricular reentry tachycardia as was elegantly demonstrated in an early study in rabbits by Janse et al. (610), and this tachycardia can be terminated by blocking I_{CaL} and $I_{K_{ACh}}$ and by adenosine (604, 611, 612).

AVN cells lack I_{to} and have background sodium inward current flowing through a nonselective cation channel (605, 613). These cells express functioning I_{Kr} , I_{Ks} , and I_f , but I_f is not required for their pacemaking (614).

4.5. Purkinje Fiber Action Potential

Purkinje fibers play a pivotal role in impulse conduction and propagation in the ventricles (615, 616). Purkinje cells can also act as subsidiary pacemakers, and they display a spontaneous diastolic depolarization, although their frequency is normally inhibited by the higher-frequency discharges of the SAN, causing overdrive

suppression. Purkinje fibers have a longer APD than do ventricular cells, and this may have a protective function against retrogradely propagating stimuli (615) but it can also represent a source of arrhythmogenic repolarization inhomogeneity, even in the normal heart, which can increase in diseased conditions or after drug exposure. In certain pathophysiological situations, Purkinje fibers can show triggered activities (617), such as EADs, DADs, and cellwide ectopic Ca^{2+} waves, in surviving tissue in the border zone of an infarct (618). It was recognized long ago that Purkinje strand fibers, which run close to or on the surface of the endocardium, are less affected by ischemia-induced tissue damage compared with ventricular cells (118, 619). Purkinje fibers have been extensively studied with the conventional microelectrode (620) and the two-electrode voltage-clamp (621) techniques. However, since cell isolation from cardiac Purkinje tissue is particularly difficult, research in Purkinje fibers has benefited less from the introduction of the patch-clamp technique, despite its importance (622).

Purkinje fibers have a special role in impulse conduction, with their depolarization being about two to three times faster (300–750 V/s) than in atrial or ventricular (100–250 V/s) muscle preparations (623). The fast depolarization is thought to be due to the abundant expression of the TTX-sensitive $\text{Na}_v1.5$ channel isoform (85), but low density of TTX-sensitive neuronal $\text{Na}_v1.1$ and $\text{Na}_v1.2$ Na^+ channel isoforms may also significantly contribute to I_{Na} in Purkinje fibers (624, 625). Importantly, the relation between impulse conduction, upstroke velocity (V_{max}), and ionic currents is not linear (626–628), and V_{max} is not a direct measure of ionic currents. I_{Na} in Purkinje fiber also seems to have a particular impact on repolarization, due to its relatively large slowly inactivating component (12, 13, 82). Some authors suggested that the skeletal muscle Na^+ channel isoform $\text{Na}_v1.4$ (78) while others suggested that $\text{Na}_v1.7$ subunits (85) were responsible for this slowly inactivating component in Purkinje fibers; however, this issue is not clarified and needs further investigations. In canine Purkinje fibers, connexin 40 is more abundantly whereas connexin 43 is similarly expressed compared with ventricular myocardium (629): this can play a role in differences between their conduction properties. The large phase 1 repolarization in Purkinje fibers (FIGURE 6) is caused by the fast inactivation of I_{Na} and activation of I_{to} . Not only is I_{to} larger than in ventricular muscle, but it inactivates somewhat slower and recovers from inactivation >10 times slower than that in the ventricular muscle cells (630). This behavior of I_{to} is attributed to the different expression of I_{to} α - and β -subunits in dog ventricular muscle and Purkinje fibers (141, 157). In human ventricular myocytes $\text{K}_v4.3$ channel subunits dominate,

whereas in human Purkinje fibers abundant $\text{K}_v3.4$ and $\text{K}_v4.3$ expressions were reported, with marked differences also in β -subunit (KChIP2, KChAP, KCNE2) expression patterns (158). The slow Ca^{2+} -dependent I_{to2} Cl^- current was also described in rabbit Purkinje fibers (631) and implicated in phase 1 repolarization and DAD formation in sheep Purkinje cells (632), since at potentials more negative than the chloride equilibrium potential chloride channels conduct depolarizing current. The L-type I_{Ca} is well expressed in Purkinje fibers and, unlike in ventricular myocytes, it is carried not only by $\text{Ca}_v1.2$ but also by $\text{Ca}_v1.3$ channels (633), and this may result in some differences in the properties of $I_{\text{Ca,L}}$ between ventricular and Purkinje myocytes. In the canine Purkinje fiber, there is larger T-type I_{Ca} , with a higher $\text{Ca}_v3.2$ expression than in ventricular and atrial myocytes (633). Based on this, it was speculated that T-type I_{Ca} has an important role in Purkinje fibers, by contributing to both depolarization and pacemaker function (634). I_{Kr} , I_{Ks} , calcium-activated K^+ currents, as well as I_{K1} have been described in Purkinje fiber (323, 635, 636). Accordingly, inhibition of I_{Kr} and I_{K1} significantly lengthens repolarization, even more so than in the ventricular muscle (615). However, the inhibition of I_{Ks} does not change repolarization of Purkinje fibers in the normal situation (256). This is not surprising, since Purkinje fibers have a plateau voltage less positive than 0 mV, which is below the activation threshold of I_{Ks} . However, at high frequencies and a high level of sympathetic activation, the plateau level is shifted toward more positive values, increasing both I_{Ks} amplitude and speed to such a level to influence both repolarization and pacemaker function (256).

Unlike ventricular but similarly to atrial muscles, Purkinje fibers express $I_{\text{K,ACh}}$ and $\text{K}_{\text{ir}3.1}$ GIRK channel subunits, thus responding with an APD shortening upon acetylcholine administration (637). The pacemaker I_f current is robust in Purkinje fibers (638–640), where it was first discovered (524), and it plays an important role in the pacemaker function. Later, a K^+ current, I_{Kdd} , was also described in Purkinje fibers (640), deactivating at more positive potentials than I_f and thus having an additional role in the pacemaker function in Purkinje fibers. In addition, spontaneous Ca^{2+} release-induced intracellular Ca^{2+} waves can also modulate normal Purkinje fiber pacemaker activity (641). This may have particular importance in ectopic automaticity of Purkinje fibers surviving myocardial infarction (618). Recently, significant SK2 current and channel expression were described in rabbit Purkinje fibers, and an important role for SK2 current in Purkinje fiber repolarization was suggested (323).

Free-running Purkinje strands emerging distally into ventricular muscle constitute a relatively large-

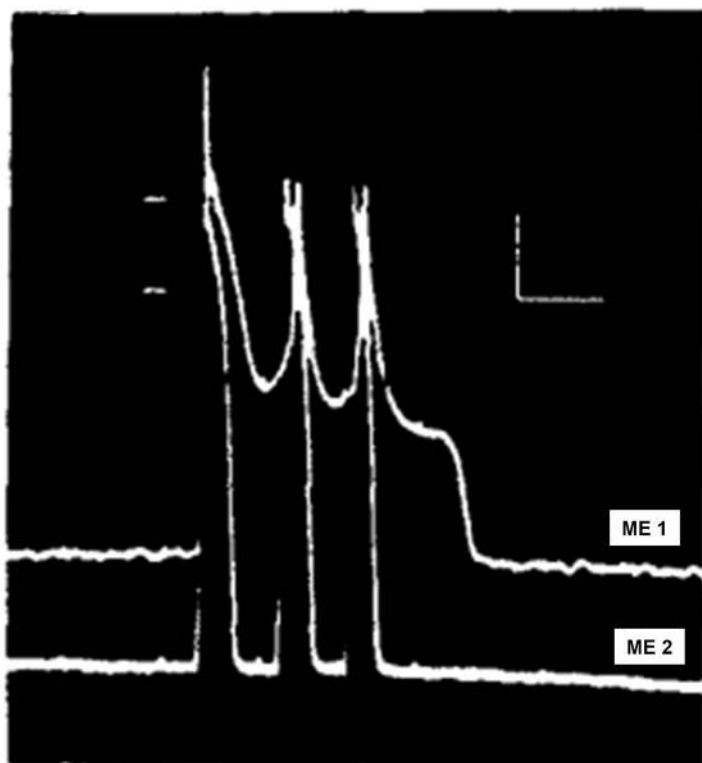
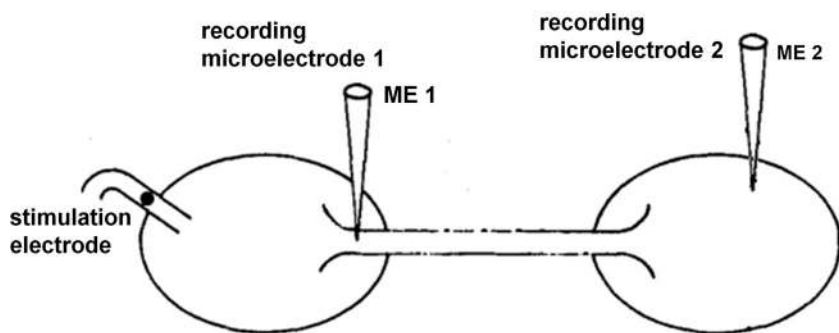


FIGURE 15. Quinidine-induced early afterdepolarizations (EADs) in canine Purkinje fibers propagate to the ventricular myocardium. *Top:* multiple EADs originating from Purkinje fiber (ME1) and propagating to the ventricular myocardium, recorded at position ME2. *Bottom:* experimental setup and the positions of the 2 microelectrodes (ME). (Modified from Ref. 643 with permission.)



resistance connection (642), and a high degree of sink for current flow, and a more favorable site of conduction block than other parts of the healthy myocardium. Also, because of the weaker electrotonic coupling, the dispersion of repolarization here can be far greater than in other places (201). Indeed, it was experimentally proven that EADs in free-running Purkinje strands could elicit extrasystoles in ventricular muscle (643) by electrotonic interaction (FIGURE 15), which is unlikely to happen in healthy and well-coupled regions within the ventricular wall.

Since Purkinje fibers are considered particularly important in arrhythmogenesis (644), further research studying Purkinje fiber ventricular muscle junctions or subendocardial layer containing a mixture of Purkinje fibers and ventricular muscle would offer promising results.

4.6. Ventricular Action Potentials: Transmural and Regional Differences

Ventricular action potentials (FIGURE 6) in humans and in most mammals have a positive (+20 to +30 mV) and relatively long plateau phase, with a small or pronounced phase 1 repolarization and notch afterwards, depending on their transmural site of origin (subendocardial, midmyocardial, or subepicardial) (143, 645, 646). Regardless of their origin, they express large I_{Na} and $I_{Ca,L}$ and relatively weak but persistent I_{NaLate} (80). These currents provide robust depolarization and thereby secure impulse conduction. In addition, by counterbalancing outward potassium currents, e.g., I_{to} , I_{Kr} , I_{Ks} , and I_{K1} , they participate in the maintenance of the plateau phase (FIGURE 6). As mentioned above, I_{Kur} and $I_{K,Ach}$ are expressed weakly or not at all in the ventricles.

There are several reports indicating electrophysiological differences between the right and left ventricle. In dog hearts, it was found that left ventricular myocytes had longer APD than those in the right ventricle (647, 648). Also, right ventricular myocytes exhibited more pronounced phase 1 repolarization and larger I_{to} (648, 649) and increased I_{Ks} (648). It was also reported that canine subepicardial and subendocardial myocytes in the left ventricle possessed larger I_{Na} with higher V_{max} compared with those in the right ventricle (650). The authors suggested that these differences provided a mechanism for the right ventricular manifestation of Brugada syndrome (650).

Almokalant, a drug with APD-prolonging effects, increased interventricular dispersion of repolarization that was associated with the occurrence of EADs and torsade de pointes arrhythmia in dogs with chronic AV block (647). In these dogs, the APD prolongation was larger in the left ventricle than in the right ventricle (647). The opposite was observed in guinea pigs, i.e., the APD-prolonging drugs dofetilide and quinidine lengthened APD more in the right ventricle (651). These findings highlight important differences among species in their responses to drugs with repolarization-prolonging effects. In humans, similarly to dogs, the APD is longer in the left ventricle with slower adaptation to increased heart rate than in the right ventricle (652). These interventricular differences in repolarization are not sufficient to cause arrhythmias in the normal heart; however, in the presence of an ischemic region at the left ventricle (LV)-right ventricle (RV) junction, the interventricular APD heterogeneity and different AP rate adaptation promote reentry arrhythmias (652).

Important regional electrophysiological differences were described in the dog ventricle long ago (653), transmurally (654), regionally (655), and in the basoapical direction (143). These differences are due to substantial differences in the density of expression of various transmembrane ion channels, shaping the action potentials accordingly in the different regions of the ventricles (645). Transmural differences in repolarization have been extensively studied and are well explored (656). It has been found that subepicardial cardiomyocytes exhibit a large phase 1 repolarization and I_{to} compared with those in the subepicardium (657). Myocytes isolated from the midmyocardium, called M cells (654), are variable in this respect, but they are still characterized by a distinct phase 1 repolarization and a relatively large I_{to} (654), I_{NaLate} (658), and NCX (659) and small I_{Ks} (660). All these ion current characteristics contribute to the longer APD of M cells compared with subepicardial and subendocardial myocytes leading to a substantial transmural dispersion of repolarization (656). Augmented transmural dispersion of repolarization has been

considered a contributor to ventricular tachycardia and fibrillation development in patients with Brugada syndrome, acquired and congenital LQT syndromes, short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT) (656). However, these differences in transmural repolarization are relatively small in the intact, undiseased ventricles (642, 661), since the neighboring myocytes are well coupled. Accordingly, experimental evidence suggests that in the intact heart the transmural dispersion of repolarization is considerably less (642, 661, 662) than that reported in tissue slices and perfused wedge preparations (663, 664). Therefore, it was argued that it is unlikely that a large, significant repolarization gradient between the subendocardium, M cells, and subepicardium existed, contributing to EADs or arrhythmias (665). However, in pathological settings and/or drug treatment and at Purkinje fiber ventricular junctions (FIGURE 15), APDs can lengthen in a nonuniform manner and cellular coupling can deteriorate, thus resulting in a substrate for serious ventricular arrhythmias.

Apico-basal electrophysiological differences have also been described: the APD was shorter and phase 1 repolarization was markedly larger in canine cardiomyocytes isolated from the apical region than in those from the basal region (655). In the same study, larger I_{to} and I_{Ks} were observed in apical than in basal cardiomyocytes (655). In this context, the apico-basal and the antero-posterior, and not the transmural, repolarization gradients have been considered to contribute to the generation of the T wave (665, 666).

Since idiopathic ventricular arrhythmias often originate from the right and left ventricular outflow tracts (RVOT and LVOT), the electrophysiological properties of these regions have also been investigated (667–670). It was found that rabbit right ventricular myocytes from the apex had longer APD, larger Ca^{2+} transients, higher Ca^{2+} stores, increased I_{NaLate} and I_{to} , but smaller I_{Kr} , L-type Ca^{2+} current, and NCX than RVOT myocytes (671). These differences were associated with increased incidence of DADs induced by pacing (671). Myocytes from the LVOT exhibited longer APD, larger I_{NaLate} and NCX, and smaller I_{to} and I_{Kr} than those from the RVOT (669).

4.7. Species-Dependent Differences in Action Potentials

Arrhythmia research is often performed in different animal models, but its ultimate goal is to understand the mechanisms in humans and to prevent, or successfully treat, arrhythmias in patients. Therefore, it should always be kept in mind how experimental results can be extrapolated to humans. It is often overlooked that rodents (rats and mice) have ion channel expression profiles

distinctly different from humans (40, 672). This also results in different cardiac electrophysiology properties (672, 673), especially during repolarization (FIGURE 12). Mice and rats have a high heart rate (600 and 400 beats/min, corresponding to cycle lengths of 100 and 150 ms), ~ 10 -fold faster than in humans. As a consequence, mice and rats have very short ventricular and atrial action potentials, to provide enough time for diastole. These short action potentials result from the presence of transmembrane currents like I_{to} and I_{Kur} (144). In the ventricles of larger mammals (guinea pig, rabbit, dog, etc.) or humans, these channels are expressed less or not at all and also have a different molecular background and functional role. Action potentials in mice or rats lack a plateau phase (144); therefore I_{Kr} and I_{Ks} are not likely to operate despite the fact that expression of mRNA for these channels has been reported (674). Notably, both I_{Kr} and I_{Ks} were observed in neonatal mouse ventricle, but after further development neither I_{Kr} nor I_{Ks} was detected in adult mouse ventricular myocytes (675). Also, inward currents like I_{Ca} and I_{Na} have different impact on ventricular repolarization than in other mammals. Consequently, drugs can have marked species-dependent effects on action potentials as demonstrated with an example of I_{Kr} inhibition in FIGURE 13. These fundamental differences mean that mice and rats can only be properly used in arrhythmia and related pharmacological research if the limitations of the models are described. As FIGURE 13 illustrates, pharmacological inhibition of specific potassium channels, such as I_{Kr} , I_{to} , and I_{Kur} , elicits strikingly different effects on ventricular repolarization in the rat, a commonly used laboratory experimental animal, compared with humans. Despite this, hundreds or thousands of papers using mice or rats have been published on this topic, because these animals are relatively cheap and easy to house. In addition, transgenic manipulations of transmembrane ion channels are almost entirely applied in mice (674), with very few exceptions (676–678). This makes the mouse a favorable target, despite the fact that the mouse can be useful to study sodium and calcium channels and connexins but not potassium channels.

There are far less consistent data on characteristic species-dependent differences in atrial action potentials and the underlying specific transmembrane currents. As FIGURE 10 shows and several papers indicate (297, 645, 679, 680), most of the species commonly used in experimental laboratories exhibit similar action potentials and underlying currents, with the atrial action potentials lacking a plateau phase, except in humans (556, 681). Human atrial tissue samples, unlike ventricular samples, can be obtained from cardiac surgery departments (from patients undergoing open heart surgery for coronary artery bypass grafting,

heart valve repair or replacement); therefore, human atrial cellular electrophysiological data are abundant, somewhat limiting the need for such studies in experimental animals.

Although the species differences in the shape of ventricular action potentials are most striking between small rodents and humans, important species differences also exist in the action potentials between humans and other mammals. Guinea pig ventricular muscle, unlike human, does not express I_{to} and does not exhibit a prominent phase 1 repolarization (144, 145); however, it expresses large I_{Ks} with distinct gating properties compared with human (3, 214, 249). Rabbit I_{to} , unlike human, is conducted mainly by $K_v1.4$ channels, and as a consequence cycle length-dependent APD is markedly different from that observed in human ventricle (682). Pig ventricular muscle exhibits Ca^{2+} -activated I_{to} chloride current that shapes phase 1 repolarization (683) but lacks 4-AP-sensitive I_{to} despite abundant expression of $K_v4.2$ and $KChIP2$ mRNA and proteins (684). The dog ventricular muscle was found to express a considerably higher density of I_{K1} compared with human (685). This results in a stronger repolarization reserve and consequently less APD prolongation upon I_{Kr} inhibition in the dog ventricle compared to human. All of these differences have a particular significance when drug effects and pathophysiological electrophysiological alterations are extrapolated from animal models to humans.

Human induced pluripotent stem cell-derived cardiac myocytes (hiPSCs) are increasingly used in cellular arrhythmia research (686, 687). This new approach is promising and expanding rapidly (688). At the present stage, however, it seems that hiPSCs have some important limitations (689). Although in hiPSCs experiments can be performed relatively fast, at present they cannot provide a substitute for carefully applied animal preparations. The so-far unresolved problems with hiPSCs are the following: data include cardiomyocytes that have not fully differentiated, still showing an immature phenotype (690, 691), and the cells spontaneously beat and often have a relatively low resting potential because they lack I_{K1} and also have low upstroke velocity (692–694). However, an interesting study suggests that the low resting potential and reduced I_{K1} are not necessarily inherent characteristics of hiPSC-derived cardiomyocytes; rather, these observations might be due to technical issues related to performing patch clamp on the relatively smaller cells (692). Also, hiPSC sarcomeres are disorganized, and their shapes are different from those of the adult cells (691). So far, atrial and ventricular-like hiPSC cells have been successfully generated, whereas SAN, AV node, or Purkinje-like stem cell generation has been unsuccessful (691). However, hiPSC-derived myocytes from patients with defined mutations using

CRISPR/Cas9-edited cells can mimic diseases (688, 695–698) that are often hard or impossible to recreate properly in animal experiments. Recent efforts to culture and continuously pace HiPSC-derived cardiomyocytes cultured in collagen gels as “engineered heart tissue” represent a new two-dimensional (2-D) and three-dimensional (3-D) approach (699–701), since it resembles more the mature myocardium. Future research in this area, however, may revolutionize the field, opening new horizons for arrhythmia research.

5. COMPUTER SIMULATIONS OF ACTION POTENTIAL

The vast quantity of experimental data describing structure and function of myocytes has enabled the development of computer electrophysiology models capable of replicating action potential and conduction properties in a variety of species including human. Thus, the last 60 yr have seen huge progress in our ability to model and simulate the electrophysiology of the heart. Cellular

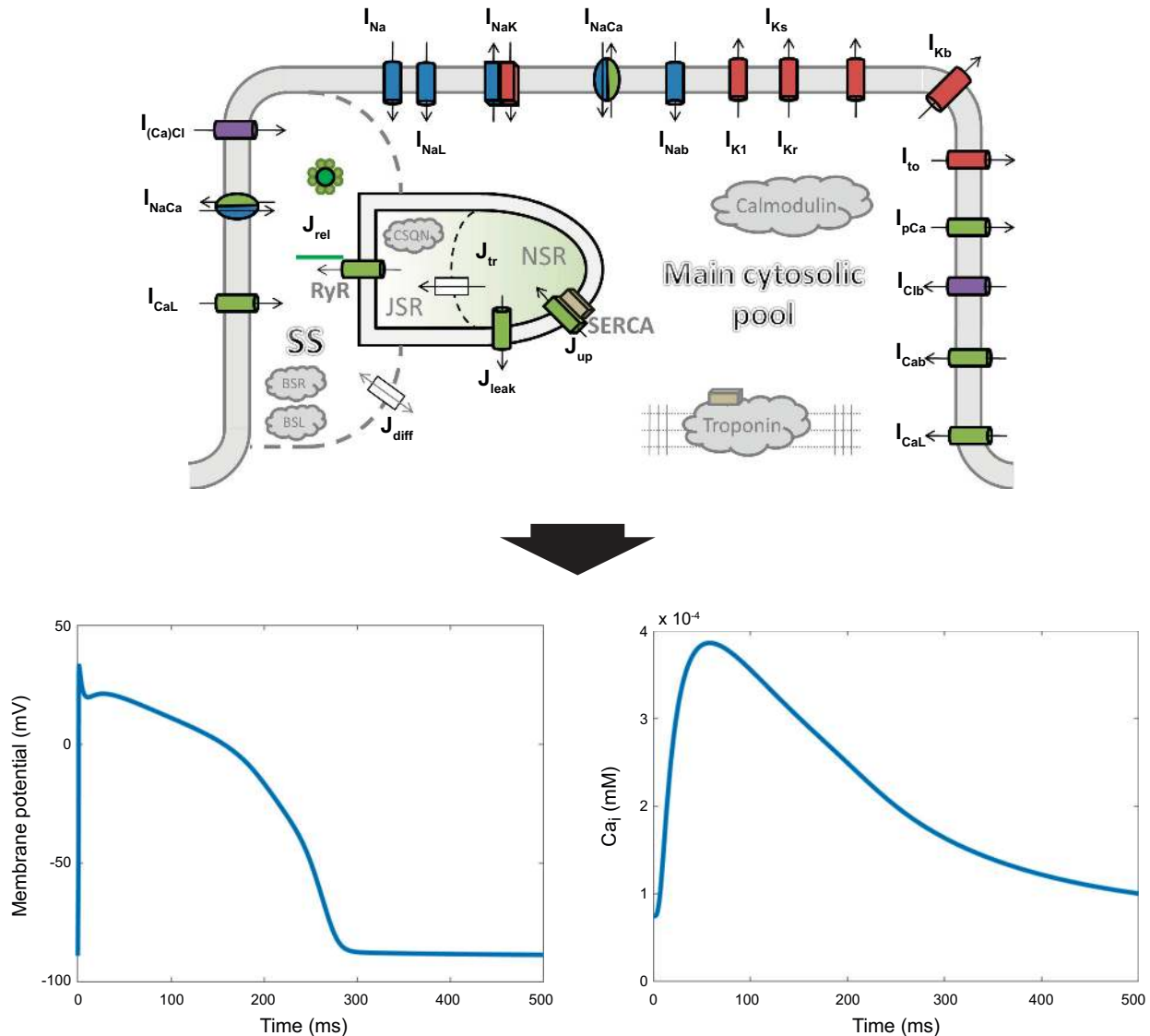


FIGURE 16. Structure of the Tomek, Rodriguez—following O’Hara–Rudy dynamic (ToR-ORd) ventricular myocyte model. The cell consists of 4 compartments: main cytosolic pool of ions, SS [junctional subspace along T tubules, where Ca²⁺ influx via L-type Ca²⁺ current ($I_{Ca,L}$) and Ca²⁺ release from the sarcoplasmic reticulum (SR) interact, and where local calcium concentrations may reach much higher values than in the main cytosolic compartment], and 2 subcompartments of the SR [network (NSR) and junctional (JSR)]. I , ionic currents; J , ionic fluxes. Clouds correspond to calcium buffers. Key effects of Ca²⁺-calmodulin kinase-II on ionic currents and fluxes (such as $I_{Ca,L}$ or SR release and reuptake) are also represented (717). Below the model diagram the simulated membrane potential and calcium transient are shown, in agreement with experimental data. RyR, ryanodine receptor; SERCA, sarcoplasmic reticulum CaATPase; CSQN, calsequestrin; $I_{Ca,b}$, background calcium current; $I_{(Ca)Cl}$, calcium-sensitive chloride current; $I_{Cl,b}$, background chloride current; I_{K1} , inward rectifier potassium current; I_{Kb} , background potassium current; I_{Kr} , rapid delayed-rectifying potassium current; I_{Ks} , slow delayed-rectifying potassium current; I_{Na} , sodium current; I_{Nab} , background sodium current; I_{NaK} , sodium-potassium pump current; I_{NaL} , late sodium current; I_{NaCa} , sodium-calcium exchange current; I_{to} , transient outward potassium current. Reproduced from Ref. 717 with permission.

computational models of different species and cell types are now available, through data and knowledge integration in an iterative process between experimental and computational work (702). The first models of a cardiac cell were the Noble model of the Purkinje cell (703) and the Beeler and Reuter model of ventricular muscle fiber (704), following the pioneering work of Hodgkin and Huxley in giant squid axon (705). Since those times, computer models have developed tremendously in their capabilities, robustness, and applications, ranging from understanding of arrhythmogenesis (706–712) to drug safety testing in industrial and regulatory settings (713–715).

Simulations with computational models offer perfect observability and controllability, which help to overcome limitations in experimental models. They can be viewed as an organized and formalized literature review that can be probed through simulation studies. They provide mechanistically informed and tractable predictions, which can then inform additional experiments and be linked back to existing knowledge of physiological mechanisms. At the same time, when simulations with a computational model fail to reproduce a particular phenomenon, gaps in knowledge or inconsistencies in the state of the art can be identified. This may be an opportunity for discovery of key factors or processes not included in the model, which may be critical for specific phenomena in living cells (716).

A computational model of cardiac cellular electrophysiology typically consists of a set of differential equations describing the mechanisms of transmembrane ionic transport and excitation-contraction coupling. Today's models are commonly separated into multiple subcellular compartments to allow localized calcium signaling and diffusion {an example of the structure of the recent human ventricular myocyte model [Tomek, Rodriguez—following O'Hara–Rudy dynamic (ORd) (ToR-ORd)] (717) is reproduced in **FIGURE 16**}.

The most broadly used framework of modeling distinct ionic currents is the Hodgkin–Huxley equations (705), where several independent “gates” (activation, inactivation, etc.) of the respective current are formulated based on experimental data; a combination of the gates then determines the fraction of open channels. This is subsequently combined with open channel conductance and ionic driving force through the open channel to produce total current. Traditionally, single-pulse square voltage clamp was used to collect data used to create ionic current models. However, in some cases it was shown that predictions based on such data do not match behavior of the current under AP clamp, such as in the late sodium current (693). Consequently, more complex protocols such as two-pulse voltage clamp, AP

clamp, or sine-wave protocols are also used to construct models with complex gating properties (718, 719). Similarly to the necessity of collecting more complex data, a mathematical model of a current sometimes requires more complex structure. There are data that cannot be represented accurately with the Hodgkin–Huxley equations, and a more sophisticated modeling method is needed. In such cases, Markov models are typically used instead, where distinct states of a channel are represented (e.g., open, closed, inactivated by voltage, inactivated by drug, etc.) along with probabilities of transitions between these states (719–721). Recently, electrophysiological measurements were combined with molecular dynamics simulation ($<0.25 \text{ \AA}$) of the channel behavior to simulate ionic currents, which may allow simulations of mutations and drug effects representing the actual molecular processes (722, 723).

5.1. Ventricular Models

Given the relevance of ventricular fibrillation, the field of computational cardiac electrophysiology has focused predominantly on ventricular cardiomyocytes. A milestone in the development of ventricular models was the Luo–Rudy model of a guinea pig cell (707, 708), setting standards in how models are constructed and evaluated based on experimental data and how such models are used to study physiological behaviors. These models include the key ionic currents, such as fast sodium current, L-type calcium current, delayed repolarization current, sodium-calcium exchanger, and the inward rectifier potassium current. The main features of calcium handling, including sarcoplasmic reticulum release and reuptake, are also incorporated. The model was subsequently used to study the interplay of ionic currents and ion concentrations in formation of early and delayed afterdepolarizations (707, 708). The Hund–Rudy canine model (724) separated the delayed rectifier currents into rapid (I_{Kr}) and slow (I_{Ks}) components (as in Ref. 725), added two components of transient outward current ($I_{to,1}$ and $I_{to,2}$), and included a model of CaMKII activation and signaling, studying the impact on rate-dependent behaviors. In addition, it introduced an intracellular subcompartment: the junctional subspace (where L-type calcium channels and ryanodine receptors colocalize and where calcium concentration reaches a much higher value than in the bulk cytosol), which is also a standard in today's models. The model was subsequently updated (726) and used to study the effect of disease (727) and of β -adrenergic stimulation (728).

Another very influential model, created in 2004, is the Shannon rabbit model (729), which also separated different components of delayed rectifier current and included the junctional subspace and which focused

predominantly on an accurate representation of calcium handling. The model was subsequently modified to improve its rate-dependent behavior (721) and was used to study alternans. Interestingly, even though a large proportion of experimental cardiac research is carried out in rodents, there are very few detailed rodent models. Relatively recent models by Bondarenko et al. (730) and Morotti et al. (731) thus provide an important tool in complementing rodent-based experimental research, and they may be used to gain insight into species differences (40).

5.2. Human-Specific Ventricular Models

Modeling and simulation of human ventricular electrophysiology are crucial subcategories of computational cardiac electrophysiology. The central species difference between human and other mammals is the high reliance of human cardiomyocytes on I_{Kr} for repolarization, unlike in other species, where the also relatively highly expressed I_{Ks} provides an additional repolarization reserve. This is of utmost importance, e.g., in the study of drug safety, where hERG/ I_{Kr} blockers may cause a much greater APD prolongation in humans than in animals (685). The specifics of human repolarization thus warrant the development of specifically human-driven computer models. The first of these that gained wide popularity was the pair of models by ten Tusscher et al. (732, 733). A second family of widely used human ventricular myocytes is the model by Grandi et al. (734) and the Carro-Rodríguez-Laguna-Pueyo (CRLP) model that followed it, focusing on rate dependence and behavior in hyperkalemic conditions (735). Possibly the currently most popular human ventricular model is the one by O'Hara et al. (ORd) (736), created and evaluated with a wide range of experimental data, many of which were collected specifically for the purpose of the model development. The ORd model incorporates CaMKII signaling and is capable of manifesting early afterdepolarizations among other features. Together with its humanlike mixture of repolarization currents, it has become, with various modifications, a dominant model in the assessment of drug safety (713, 715) and is a prime example of how computer modeling and simulation may be used for regulatory purposes (737). Recently, a new human ventricular myocyte model, ToR-ORd, was published (717), improving on its predecessor ORd in multiple aspects, such as similarity of the action potential morphology to experimental data or the response to sodium channel blockers. The model also brought biophysical insight into properties of $I_{Ca,L}$ and I_{Kr} , which are important for the understanding of sodium and calcium dynamics in ventricular myocytes.

5.3. Other Tissue-Specific Modeling

As discussed in sect. 4 of this review, different tissues manifest markedly different action potentials, achieved by differential function of ionic currents. Cardiac models reflect this, allowing tissue-specific simulations representing specific features of atrial, Purkinje, or sinoatrial cells.

5.3.1. Atrial models.

Human atrial electrophysiology modeling and simulations are active topics of research. Two prominent models of human atrial electrophysiology are by Courtemanche et al. (738) and Nygren et al. (739), both recapitulating specific AP morphology of atrial myocytes. The Courtemanche model used the Luo–Rudy94 model as a starting point (708) but reformulated the ionic currents according to human and canine data from atrial myocytes. The model was used to understand the importance of L-type current inactivation in APD shortening in the S1S2 protocol and to gain insight into the role of I_{to} in variability of atrial AP morphology. The Nygren model (739) was mostly based on a similar set of data, but it used a different model as the starting point (740). Its analysis provided insight into differences between human and rabbit repolarization, focusing on the role of the sustained outward potassium current. More recent models, adding and studying ionic homeostasis, additional currents, and signaling, are described in Refs. 741–743. We refer the reader to more comprehensive reviews (744–746) on atrial modeling and simulation.

5.3.2. Purkinje cell models.

Even though Purkinje fiber cells were the focus of the first cardiac electrophysiology models (703), progress in this area has been irregular. In 1985 an updated model was published, describing both electrophysiology and changes in ionic concentrations (639), but the focus subsequently shifted toward other cell types discussed above (747). In recent years, the interest in Purkinje fibers has been reinvigorated, producing models focusing on their role and changes in heart failure (748), the electrophysiological basis of rabbit Purkinje electrophysiology (749), and the importance of Purkinje fibers in arrhythmogenesis (750, 751). The very recent Purkinje model by Trovato et al. (752) introduced a comprehensive calibration to human data in a wide range of conditions, bringing insights into Purkinje cell EADs and abnormal automaticity such as following I_{K1} reduction or I_f increase.

5.3.3. Sinoatrial cell models.

Sinoatrial cell modeling and simulation has also made significant progress in recent years in both rabbit (753, 754) and human (755), enabling investigations into the ionic basis of the cardiac pacemaker in normal and disease conditions including the effect of mutations (281, 755, 756).

5.3.4. hiPSC models.

An additional cell type that is gaining increasing popularity is human-induced pluripotent stem cells (hiPSCs), which offer a new human-based paradigm in experimental research. Computer modeling and simulation of hiPSC is an important tool complementing the experimental system. This was pioneered by Paci et al. (757) and is now an active research field (758, 759).

5.4. Different Modeling Scales

In sect. 5.3, we focused predominantly on cell-level modeling, where one set of equations describes the cellwide current. This usually provides a good trade-off of relatively high biological detail but still affordable computational time (<1 s per 1 action potential). For specific purposes, it may be necessary, however, to either increase or decrease the level of detail. In particular, detailed phenomena driven by cellular calcium handling (such as calcium waves and resulting delayed afterdepolarization as well as some mechanisms of calcium-driven alternans) usually require a high degree of detail (760–762). In such models, a single cell is subdivided into small (microscale or even nanoscale) cuboids that may represent membrane, calcium release units from the SR, cytosol, etc. and are coupled together to represent the cell. Such a level of detail, however, considerably increases computational time, such as hours (microscale models) or more than a day (nanoscale) for several beats on a personal computer. On the other side of the spectrum of model complexity are models such as the Fenton–Karma (763) and minimal ventricular (MV) (764) models, which are more than an order of magnitude faster to simulate compared with biologically detailed cellular level models. This makes such models an attractive tool, for example, model personalization using clinical electrophysiological recordings (765) or when tissue properties (rather than ionic properties) are the target of the investigations (766, 767).

5.5. Variability in Computer Models

In recent years, representing variability in cardiac models has emerged as a key new concept (50, 768–773). There

are multiple sources of variability in experimental and clinical data, caused by both intra- and interheart differences as well as differences in experimental settings and/or measurement techniques (50). One of the techniques to investigate potential causes and modulators of biological variability is the use of populations of models rather than a single generic computational model (768, 774, 775). Populations of models are ensembles of models sharing the same structure based on a particular cardiomyocyte model (such as the O'Hara–Rudy model) but with variations in model parameters, such as the conductances of ionic currents. To achieve plausible populations, a calibration to experimental or clinical data can be carried out (768): e.g., a model is accepted in a population only if its action potential morphology and calcium transient properties fall within an experimentally observed range. Such calibrated populations have proven to be useful in the study of hypertrophic cardiomyopathy (776) and atrial fibrillation (775, 777) and for drug safety assessment (715, 775). An intrinsic limitation is that a plausible phenotype may be produced by an unplausible mechanism and/or by a biologically unrealistic combination of conductances of ionic currents. More comprehensive data collection, reporting, and understanding of biological variability is thus an important future step for the fields of both experimental and computational cardiac electrophysiology.

6. CELLULAR ARRHYTHMIA MECHANISMS

6.1. Depolarization Abnormalities

Impaired depolarization capability in cardiomyocytes can reduce conduction safety, providing proarrhythmic substrate and potentially contributing to conduction block and reentry arrhythmia. One example of depolarization abnormality leading to reentry arrhythmia is the Brugada syndrome, caused by the loss of function of *SCN5A* (778, 779). It should be noted, however, that in patients with Brugada syndrome the mechanisms of arrhythmia are more complex, since decreased function of L-type I_{Ca} and enhanced function of I_{to} also contribute to the development of phase 2 reentry (780), due to enhancement of dispersion of repolarization across the ventricular wall (779).

Ischemia can cause regional membrane depolarizations, which indirectly decrease the strength of I_{Na} by eliciting partial or full channel inactivation and result in slowing of impulse conduction or unidirectional or bidirectional conduction block. All of these factors are considered important in arrhythmogenesis. However, their detailed discussion is beyond the scope of this review, since they are described by others in great detail (31, 781–785). Drugs that inhibit I_{Na} can have similar effects and can also cause reentry arrhythmias (202, 786, 787).

Upregulation of the I_f current (788) and HCN channels (789) in the ventricles and atria (790) was reported in HF (789) and HCM (791, 792). These changes can cause abnormal myocardial depolarizations, and they can relate to increased incidence of ectopic beats, providing possible triggers for arrhythmias in an environment where dispersion of repolarization (arrhythmia substrate) is already augmented by structural heart disease.

6.2. Triggered Automaticity

Abnormal myocardial automaticity (formation of propagating spontaneous action potential) is an established trigger contributing to arrhythmia onset (26). One particular type of such automaticity closely linked to disturbance of normal cellular electrophysiology is the so-called “triggered automaticity,” which requires preceding action potentials that are essential for the subsequent spontaneous firing (793). Depending on the temporal relationship between such depolarization and the preceding action potential, triggered automaticity is typically separated into early and delayed afterdepolarizations.

6.2.1. Early afterdepolarizations.

Early afterdepolarization (EAD; **FIGURE 10, A** and **B**) is characterized by depolarizing potential changes occurring before the termination of the preceding action potential during phase 2 or phase 3 repolarization. EADs are usually generated when action potential duration is excessively prolonged, e.g., when I_{Kr} is impaired. As a consequence of the lengthened action potential, those L-type calcium channels that have already recovered from inactivation can reopen, and some of the calcium channels carry a Ca^{2+} window current (707, 708), causing positive voltage oscillations during the plateau (phase 2 EAD) or terminal repolarization (phase 3 EAD). The Luo–Rudy studies (707, 708) also proposed a second type of EADs, phase 3, resulting from spontaneous calcium release during repolarization, which then translates into depolarization via NCX. The relevance of this mechanism was subsequently demonstrated experimentally in Purkinje fibers (131). This type of EAD strongly resembles delayed afterdepolarizations in its mechanism but differs in the timing (during AP vs. after AP). Both types of EADs are rate dependent, with the reactivation-driven mechanism appearing predominantly at slow pacing, whereas the release-driven EADs occur at fast pacing (794).

In general, both the L-type calcium current and NCX are known to act synergistically in EAD formation (795, 796), and the controllability of computational models has been used to understand their interplay. For

example, Kurata et al. (797) demonstrated how NCX contributes to EADs in the popular O’Hara–Rudy model (736) via two distinct mechanisms. First, the influx of calcium via the L-type calcium current upon its reactivation translates into calcium efflux via NCX and thus additional inward current (which can, in turn, promote further activation of L-type calcium current). Second, NCX expressed adjacent to L-type calcium channels acts as a “sanitizer” of calcium in the cellular region, removing calcium ions from the junctional subspace during repolarization. This may subsequently reduce the calcium-dependent inactivation of L-type calcium current, facilitating earlier reactivation. The insight into EAD origins is not limited to L-type calcium current and NCX; nonequilibrium gating of late sodium current was implicated in EAD formations (798). The increased availability of data on signaling pathways has also enabled computationally driven insights on how EADs are facilitated via CaMKII- or PKA-driven pathways (799). This is particularly important for our understanding of EADs in disease conditions such as heart failure, where these pathways are dysregulated.

One interesting involvement of I_{Kr} in EAD formation beyond the role in APD prolongation lies in its dynamic of activation and reactivation. Lu et al. (719) used a range of electrophysiological protocols to demonstrate an intriguing interplay of I_{Kr} activation, inactivation, and recovery from inactivation, which leads to rapid increase of I_{Kr} during late-plateau reactivation, such as during an EAD. Such an increase in repolarizing current would be expected to counteract and potentially outweigh depolarizing currents, potentially preventing the formation of a larger-amplitude EAD.

6.2.2. Delayed afterdepolarizations.

The delayed afterdepolarization (DAD) is characterized by depolarizing potential changes following the termination of the preceding action potential (129, 130, 632) during diastole (**FIGURE 10C**). DAD is generally attributed to calcium-sensitive depolarizing currents after spontaneous Ca^{2+} release from the SR during Ca^{2+} overload, or CaMKII-dependent phosphorylation (800, 801), which is promoted by diseases like chronic AF, ischemia, heart failure (801–803), and catecholaminergic polymorphic ventricular tachycardia (CPVT) or drugs like digitalis. The most important calcium-sensitive current implicated in DAD formation is the forward-mode NCX, but a role for the calcium-sensitive chloride current has also been suggested (804). The calcium-induced depolarization is opposed primarily by I_{K1} , which tries to maintain resting potential (805). When the depolarization induced by calcium-sensitive currents is of sufficient magnitude, overcoming I_{K1} , it activates I_{Na} , triggering a new action potential. Automaticity occurring in the pulmonary veins

and in the myocytes represents important abnormal impulse formations, and at present it seems that their cellular mechanisms are complex, including the possibility of DAD and EAD generation as well (FIGURE 14).

The spontaneous calcium release is a stochastic phenomenon, represented by calcium sparks (806, 807) and intracellular calcium waves (807–810), and multiple calcium release sites need to synchronize to produce a cellwide calcium release (811, 812). The stochastic nature of such events as well as generally limited controllability and observability of subcellular calcium handling in the experimental setting, complicate detailed understanding of their origins. On the other hand, computer models (736) offer excellent controllability and observability and thus are a popular tool to understand origins of spontaneous calcium release and ultimately DADs. Increasing availability of subcellular experimental data has enabled the construction of spatially detailed models, where the cell is subdivided into up to hundreds of thousands of subdomains with separate clusters of potentially stochastic ryanodine receptors (760, 813, 814). As a result, such models can give very detailed predictions, elucidating how originally random calcium sparks are recruited into calcium waves and ultimately DADs but also giving explanations for DADs that do not rely on calcium waves (814).

6.2.3. From afterdepolarizations to arrhythmic behavior.

One important aspect of triggered automaticity is that the role of EAD and DADs in arrhythmogenesis is most likely overestimated in single-cell experiments versus the intact heart. Even in relatively poorly coupled tissue, electrotonic interactions with neighboring cells will decrease the depolarization produced by an EAD or a DAD. However, moderate uncoupling will decrease the electrotonic interaction between a focus and the surrounding cells and can actually favor action potential propagation (815).

Computer simulations studies have significantly contributed to the understanding of the conditions under which the afterdepolarizations of single cells may translate into propagation throughout myocardium (816). These modeling studies showed that when simulating healthy cells and their afterdepolarizations, ~70 cells manifesting an afterdepolarization are needed to trigger excitation in a fiber, ~7,000 in 2-D tissue, and ~700,000 in 3-D tissue. The specific numbers may very well vary with numerical aspects related to the simulations, such as the mesh discretization, but this nevertheless suggests the unlikelihood of EADs or DADs promoting into tissue reactivation in a healthy tissue. At the same time, however, the study by Xie et al. (816) also

investigated the effect of gap junction uncoupling, fibrosis, and heart failure-like remodeling, showing that the combined effect may reduce the number of cells needed for an afterdepolarization-driven propagation by two orders of magnitude. Specific patterns of uncoupling, such as thin strands of myocytes within postinfarction scars (817), which are similar to a fiber with regard to coupling, may increase the relevance of afterdepolarizations of arrhythmia even further. Another type of weakly coupled tissue that might enable synchronization of afterdepolarizations is the endocardial Purkinje ventricular junctions, as mentioned above (FIGURE 15).

In addition to promotion of extrasystolic reactivation via cell decoupling, other mechanisms of synchronization of afterdepolarizations are via stretch-activated channels (818), current flow in the border zone of acute ischemia (706), and partial chaos synchronization (369). In a modeling study of calcium-driven afterdepolarizations, it was suggested that calcium waves also synchronize by calcium flux through gap junctions (819); however, experimental results argued against this possibility (811). Ultimately, simulation studies have shown that the baseline risk of EADs may be considerably increased in diseased conditions (776, 820), further facilitating translation of a depolarization to tissue activation.

In the case of increase in intracellular calcium during elevated sympathetic drive and/or diseases like heart failure or catecholaminergic polymorphic ventricular tachycardia (CPVT) (821), Ca^{2+} overload may occur and the SR can become leaky and release additional Ca^{2+} (822). Mutations in the gene encoding the cardiac ryanodine receptor-related Ca^{2+} release channels (RyRs) can cause extrasystole and serious tachycardia such as CPVT by abnormally releasing Ca^{2+} from the SR (823) into the cytosol on the response of catecholamines which Ca^{2+} would activate the electrogenic forward NCX depolarizing cells beyond their threshold of activation. In a recent study, in a new model for CPVT in engineered human tissue fabricated from human pluripotent stem cell-derived cardiomyocytes, high-frequency pacing and isoproterenol administration increased Ca^{2+} wave propagation heterogeneity and elevated intracellular $[\text{Ca}^{2+}]_i$, leading to local depolarizations and conduction block (creating the arrhythmia substrate), and subsequently resulting in reentry (700). Similarly to CPVT, leaky ryanodine receptor-related Ca^{2+} release channels were also reported in heart failure (802, 824).

6.3. Frequency Dependence and Restitution

It was observed long ago that action potential duration and impulse conduction depend on heart rate or on the stimulation frequency. To study frequency-independent repolarization changes caused by disease, drugs, or any

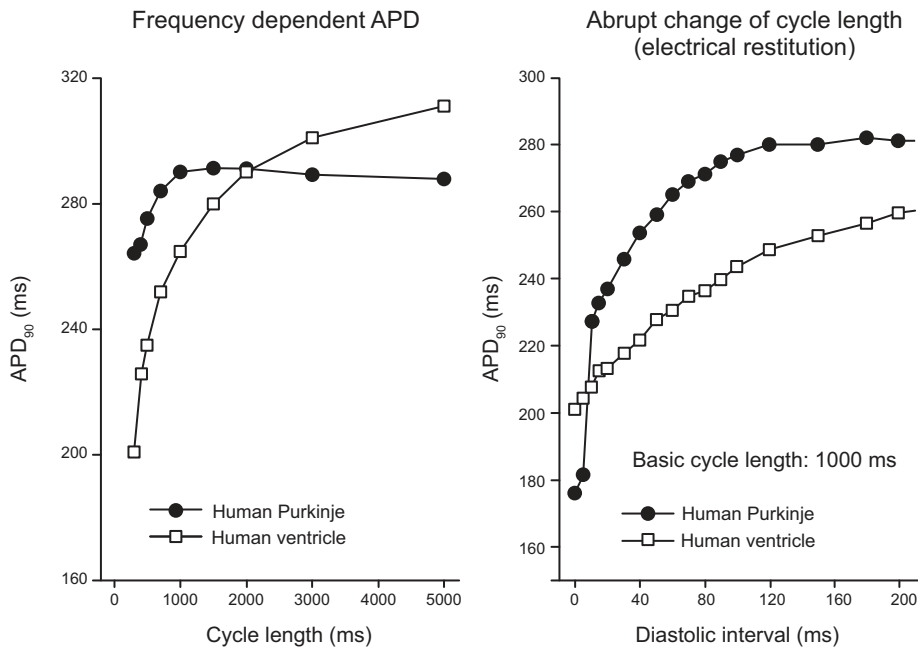


FIGURE 17. Cycle length-dependent action potential duration (APD₉₀) changes (*left*) in undiseased human (donor) ventricular muscle (open symbols) and Purkinje fiber (filled symbols) preparations. *Right*: the relationship between APD₉₀ and the preceding diastolic interval (S1S2 restitution) in human ventricle (open symbols) and Purkinje fibers (filled symbols). Both protocols were measured with the conventional microelectrode technique. APD₉₀, APD at 90% repolarization. Unpublished observations from our laboratory at the Department of Pharmacology and Pharmacotherapy, University of Szeged, Hungary.

other factors, correction formulas have been used to estimate QT intervals corrected for heart rate (QTc) on the ECG. At elevated heart rate, extracellular K⁺ accumulation may occur in the clefts, slightly depolarizing the resting membrane potential that slows impulse conduction and impairs safety of impulse propagation. At extrasystoles early following the end of ERP, repolarization is still not fully terminated and Na⁺ and Ca²⁺ channels are partially inactivated, resulting in less depolarizing current and

decreased safety or slowed impulse propagation. Frequency-dependent APD changes show general patterns (682, 825–830) that APD is short at high and longer at slow constant rates (FIGURE 17). The frequency dependence of APD shows substantial species, tissue, and regional variation and has important implication for arrhythmogenesis. At slower heart rate, APD can be markedly prolonged, favoring triggered arrhythmias via EAD formation, and may also result in enhanced

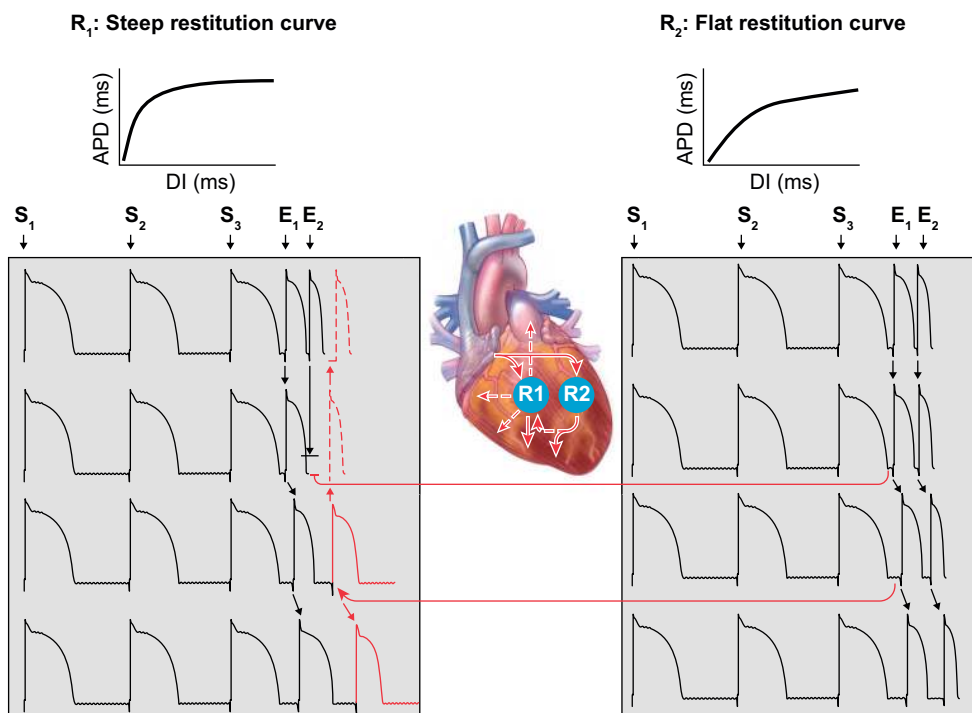


FIGURE 18. Arrhythmia development via regional differences of the action potential (AP) restitution. *Left*: consecutive action potentials from a region with a steep restitution curve (R₁). *Right*: a region with flat action potential duration (APD) restitution (R₂). In both cases, S₁–S₃ indicate 3 consecutive sinus node stimuli followed by 2 extra stimuli (E₁ and E₂). In the case of steep APD restitution, the E₁ is able to propagate while the conduction of E₂ is blocked since the refractory period of the developed extra AP is sufficiently long. In contrast, in the flat restitution region both extra stimuli will propagate, since the APD of the extra beats are not markedly prolonged. Therefore, these APs can reach the R₁ region (red arrow) and evoke extra beats where the refractory period has already been terminated (red curves), establishing a circulating movement of impulse propagation. DI, diastolic interval.

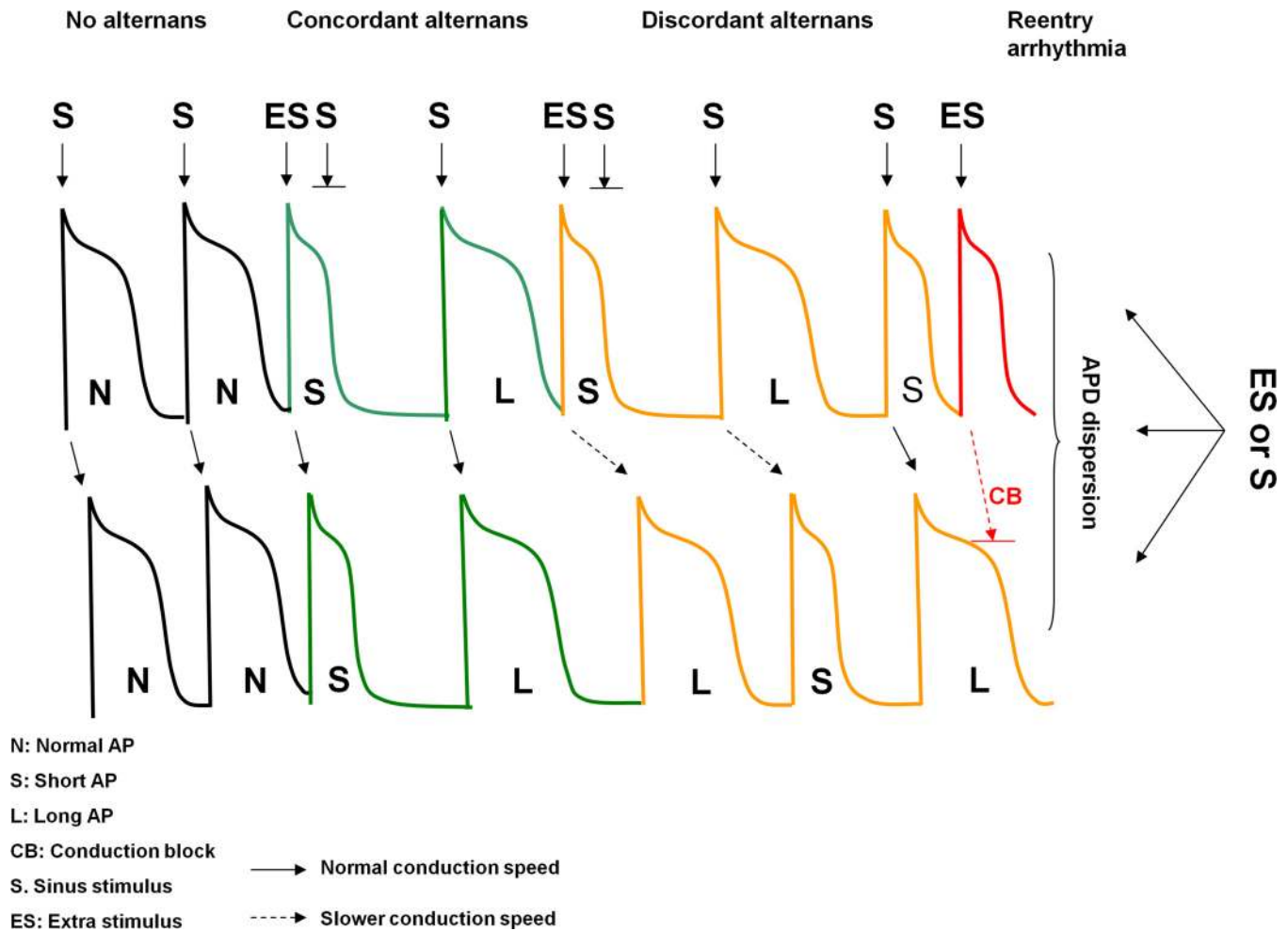


FIGURE 19. Proposed mechanism of action potential (AP) alternans and arrhythmia development. The *top* sequence of the AP illustrates a proximal and the *bottom* sequence a distal area of the left ventricle in respect of impulse propagation. On *left*, 2 consecutive normal (N) action potentials are shown; the depolarization is readily conducted toward the distal area (black arrows), evoking further APs. When an extra stimulus (ES) with short coupling interval reaches the proximal area, the evoked APs will be organized as a short-long-short pattern in both regions, establishing concordant alternans (green curves). Under this condition, a second extra beat will evoke a short AP in the proximal region but a long AP in the distal area, since the refractory period causes slowed impulse propagation (discordant alternans, orange curves). In this case the heterogeneity of the repolarization causes a third extrasystole (red curve) in the proximal region to be blocked in the distal area (red dashed arrow), providing possibility for development of reentry arrhythmia. APD, action potential duration.

substrate for arrhythmias by increasing dispersion of repolarization.

Electrical restitution refers to the recovery of the APD of an interpolated beat as a function of time following the previous beat. This changes in a manner that is somewhat similar to that seen (831) during frequency-dependent steady-state APD changes (FIGURE 17, *left*). Despite the similarities, there are important differences (FIGURE 17, *right*) that warrant the restitution being studied as a separate rate-dependent property (826, 827, 832–835), with importance for arrhythmia research (20, 836). According to the restitution hypothesis, as the diastolic interval increases because of the propagation of an extra beat, the second extrasystole would encounter longer APD/ERP and local conduction block may occur. A steeper restitution curve would favor such an effect and

is considered proarrhythmic (20, 662, 837, 838), whereas flattened electrical restitution curves would have an opposite consequence (FIGURE 18). Local regional differences in the APD restitution curves (839) may also favor arrhythmogenesis (840). The ion channel background of cycle length-dependent APD changes including APD restitution is attributed to the incomplete recovery and/or deactivation of different inward (I_{Na} , $I_{Ca,L}$) or outward (I_{to} , I_{Kr} , I_{Ks} , I_{Cl}) currents based on the gating behavior of these channels (841, 842). In addition, intracellular ion concentration changes for Ca^{2+} and Na^{+} rapidly or slowly would activate electrogenic NCX or Na^{+} - K^{+} pumps. Also, frequency changes can result in significant alterations in extracellular K^{+} concentration in the extra-cellular clefts (843), causing changes not only in depolarizing but also in repolarizing transmembrane ionic currents. Detailed

discussion of these mechanisms is beyond the scope of this review.

6.4. Repolarization Alternans and Temporal Repolarization Variability

Repolarization alternans (FIGURE 19) at the cellular level manifests as oscillation of long and short APD at rapid heart rates, typically with concurrent oscillations in calcium transient amplitude (712, 844). It has been demonstrated that alternans can precede the formation of arrhythmia in the heart (845, 846). Multiple studies and reviews explain the mechanisms of arrhythmia induction following alternans, typically linked to increased dispersion of repolarization (712, 847, 848). The spatial pattern of alternans across cardiac tissue is typically “concordant” at submaximal heart rates, i.e., the APD is either simultaneously shortened or prolonged in all sites (FIGURE 19) (712). However, further increase in the pacing rate can elicit so-called discordant APD alternans (FIGURE 19), when APDs at more distant regions can alternate with opposing phases (712), substantially increasing dispersion of repolarization and thereby the substrate for arrhythmias (849).

The fact that repolarization alternans typically occurs together with underlying oscillation of calcium transient amplitude (850, 851) poses the question of which of these two drives the other.

The first hypothesis suggests that the steep slope of APD restitution is the alternans driver (852), and this mechanism of arrhythmia is replicated by the ten Tusscher–Noble–Noble–Panfilov model of human ventricular myocyte (732, 733). As mentioned above, the ion channel background of APD alternans is attributed to the incomplete recovery and/or deactivation of different inward (I_{Na} , I_{Ca}) or outward (I_{to} , I_{Kr} , I_{Ks} , I_{Cl}) currents based on the gating behavior of these channels (841, 842). In addition, intracellular ion concentration changes for Ca^{2+} and Na^+ rapidly or slowly would activate electrogenic NCX or Na^+ - K^+ pumps. Also, frequency changes can result in significant alterations in extracellular K^+ concentration in the extracellular clefts (843), causing changes not only in depolarizing but also in repolarizing transmembrane ionic currents.

On the other hand, other studies suggested that oscillations in the calcium transient amplitude are the primary alternans driver (851, 853). Such oscillation of calcium transient can be subsequently translated into APD alternans by NCX and other calcium-sensitive currents. Calcium-driven alternans was first suggested to originate from a Ca^{2+} release-reuptake mismatch due to the steep dependence of Ca^{2+} release on SR loading (851, 854). While in good agreement with a majority of experimental data, the experiments by Picht et al. (855)

suggested that refractoriness of the ryanodine receptor rather than release-reuptake mismatch may underlie at least some of the observed alternans. Such a mechanism is also supported by certain computer models and may be either due to the refractoriness of the channel or due to changes in calsequestrin conformations with subsequent RyR block from within the SR (761). In a recent study utilizing iterated maps as well as a spatially detailed myocyte model, Qu et al. (856) showed that both mechanisms may act synergistically to promote alternans. A third explanation of calcium-driven alternans is the alternans driven by sarcoplasmic reticulum calcium cycling refractoriness (SRCCR) (857, 858). SRCCR alternans arises from a combination of steep load-release relationship (similar to release-reuptake mismatch hypothesis) and refractoriness of the SR release (similar to RyR refractoriness hypothesis). However, the latter does not result from an intrinsic RyR refractoriness but is a result of a limited rate of refilling of releasable calcium in the junctional SR. This mechanism underlies alternans in the Rudy-family models (728, 736, 857).

Alternans typically occurs only at rapid heart rates; however, data from human hearts show that in some cases alternans manifesting at rapid heart rate may cease with a further increase in pacing frequency (“eye-type alternans”) (859). The eye-type pattern was replicated with a populations-of-models approach (859), with the mechanism of the eye closure at rapid pacing being linked to flattening of the SR load-release relationship in certain conditions (858). Using a spatially distributed model of calcium handling, Qu et al. (856) also observed eye-type alternans in simulations where sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA) pumps were downregulated.

One important question pertaining to the spatial pattern of alternans in tissue is what determines whether alternans manifests in the relatively benign spatially concordant pattern or the highly proarrhythmic discordant one. Pastore et al. (849) observed in their experiments that nodal lines (lines in tissue separating areas of opposing alternans phase) were associated with structural abnormalities. However, discordant alternans may arise even in tissue with no obvious structural abnormality. Computer models provide two explanations of this phenomenon. Qu et al. (860) have shown that discordant alternans may emerge as a result of conduction velocity restitution. This explanation is characterized by the radial pattern of nodal lines with regard to pacing site. The second explanation by Sato et al. (762) relies on tissue synchronization of discordant alternans arising at the subcellular level. This explanation does not rely on a particular pattern of nodal lines and can explain experimental observations in Ref. 847.

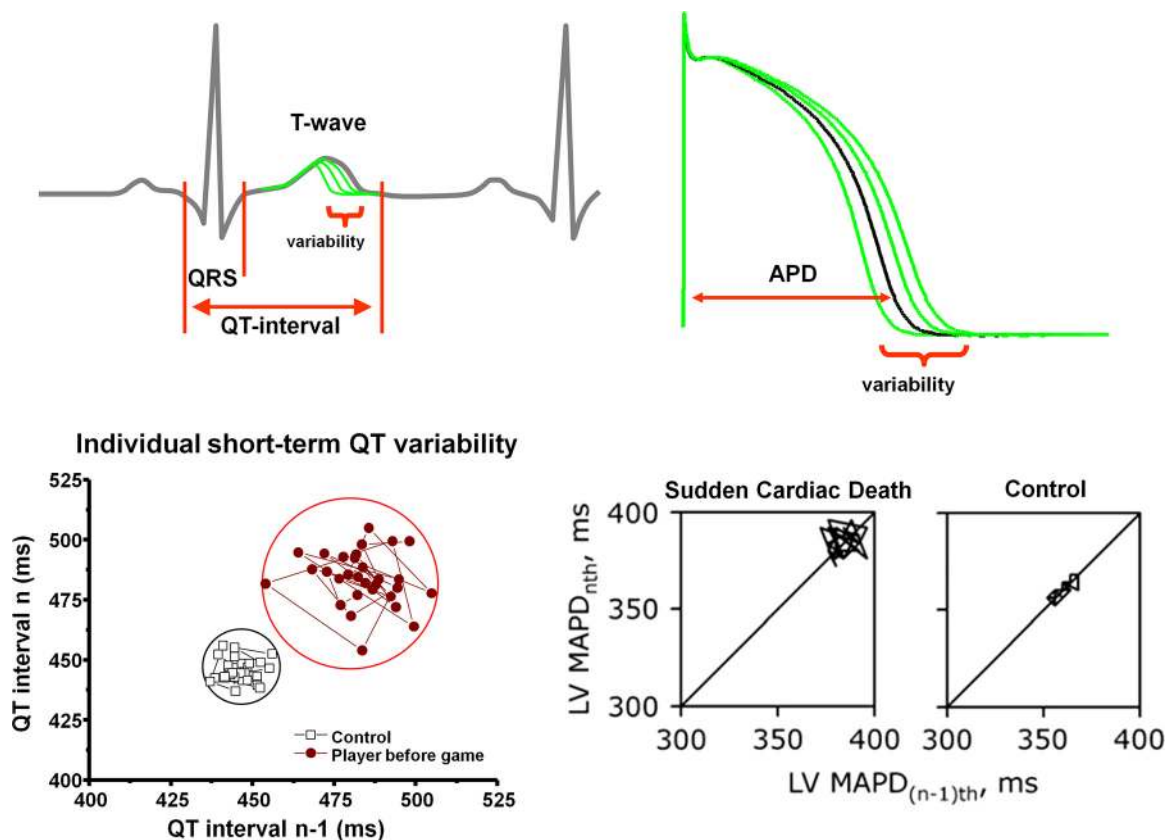


FIGURE 20. Short-term temporal variability of repolarization and the risk of sudden cardiac death (SCD). *Top left:* schematic illustration of QT interval variability on an electrocardiogram trace. *Top right:* schematic illustration of action potential duration (APD) variability. *Bottom left:* increased QT interval short-term variability in a representative professional soccer player compared with a control individual, illustrated on a Poincaré plot, where each QT interval n is plotted against its former value, $n - 1$. *Bottom right:* individual Poincaré plots illustrating increased short-term variability of left ventricular (LV) monophasic action potential duration (MAPD) in chronic atrioventricular block dogs with SCD compared with control dogs without SCD. (Modified from Ref. 861 with permission.)

Spontaneous episodes of ventricular tachyarrhythmia in patients are often preceded by a short-long-short sequence of cardiac cycles or irregular beat-to-beat variation of the QT intervals. This temporal instability of repolarization measured as short-term APD or QT variability similarly to spatial repolarization inhomogeneity is considered as an important marker for proarrhythmia (250, 861) (FIGURE 20). The mechanisms of short-term APD variability are not fully understood; however, they may relate to the stochastic behavior of the ion channels underlying the action potentials or the fluctuation of the intracellular Ca^{2+} movements and its electrophysiological consequences (822).

7. ION CHANNEL AND ACTION POTENTIAL REMODELING IN ACQUIRED CONDITIONS

Certain diseases and alterations in physiological functions evoke changes in the heart that are collectively termed remodeling (7). Remodeling can also affect the

densities or functions of transmembrane ion channels and/or pumps, so-called electrical remodeling (TABLE 2) (7). Thus, electrophysiological remodeling is the result of changes in the expression of ion channels and pumps, and it can affect both repolarization and impulse conduction. In parallel, remodeling often affects the structure of cardiac tissue, which can be detected by microscopy (880). Structural remodeling includes fibrosis and wound healing, resulting mainly from the activity of fibroblasts and myofibroblasts (681, 881, 882). Fibrosis and scars impair impulse conduction, eliciting conduction blocks, changing the directions of normal impulse propagation, and enhancing the heterogeneity of impulse conduction. Finally, remodeling of the postinfarction border zone includes alterations to the pattern and function of gap junctions, further increasing heterogeneity of conduction (883). The combined effects of electrical and structural remodeling increase the propensity of reentry-based arrhythmias.

In this section, electrical remodeling following from the best-explored and probably most important

Table 2. Remodeling of transmembrane currents/transporters in disease

Current	AF-Atrial Muscle		HF-Ventricular Muscle		DM-Ventricular Muscle	
		Reference		Reference		Reference
I_{Na}	↓	7	↓	7, 862	↓	863,864
I_{NaL}			↑	126,127		
$I_{Ca,L}$	↓	7	∅		∅ slow inactiv.	865
I_{to}	↓	7, 549	↓	7, 156, 159, 866	↓	271, 867,868
I_{K1}	↑	205	↓	7, 157		
I_{Kr}			↓	7	↓ ∅	271, 867, 869
I_{Ks}			↓	7	↓	271, 867
I_{Kur}	↓ ∅	549, 870				
$I_{K,ACh}$	↑	358, 584, 871				
I_{KCa} (SK2)	↑	562, 872	↑	315, 873	↓	874
I_f			↑	788,789, 875,876		
NCX			↑	7, 365		
Connexin	↓	7	↓	877–879		

AF, atrial fibrillation; DM, diabetes mellitus; HF, heart failure; $I_{Ca,L}$, L-type Ca^{2+} current; I_f , funny/pacemaker current; $I_{K,ACh}$, acetylcholine-activated potassium current; I_{KCa} , calcium-activated potassium current; I_{Kr} , rapid component of delayed rectifier potassium current; I_{Ks} , slow component of delayed rectifier potassium current; I_{Kur} , ultrarapid component of delayed rectifier potassium current; I_{K1} , inward rectifier potassium current; I_{Na} , sodium current; I_{NaL} , late sodium current; I_{to} , transient outward current; NCX, Na^+/Ca^{2+} exchanger.

diseases is briefly summarized in order to better understand the mechanisms of cardiac arrhythmias.

7.1. Remodeling in Atrial Fibrillation

AF is the most common sustained arrhythmia in the developed world, and its prevalence increases with age, exceeding 10% after the age of 80 yr (6, 884). AF itself is seldom directly life-threatening and usually has few acute hemodynamic consequences, but it represents a high risk for thromboembolism and stroke given an increased risk of thrombus formation in the hypodynamic atria (885). It can furthermore contribute to the development of heart failure; therefore AF has great significance in cardiovascular morbidity and mortality (886).

Studies performed in atrial tissue originating from chronic AF patients or experimental animals show significantly shorter and often triangular-shaped action potentials compared with those obtained from sinus rate patients and animals. It must be emphasized that data regarding electrophysiological remodeling can be controversial. For example, in pacing-induced AF in

dog hearts, atrial APD is abbreviated less (1135) than those observed in human (7, 309). This emphasizes the importance of the substantial species differences mentioned above, in this case between dog and human atrial action potential waveforms (FIGURE 12). Therefore, the interpretation of results based on animal experiments should be considered with care in not only pharmacological but pathophysiological studies as well.

High atrial rate or tachypacing in experimental animals induces atrial remodeling (7, 363, 777, 887, 888) that is characteristic for chronic AF. Atrial extrasystoles or electrical stimulation can easily induce AF in remodeled atria, and the longer and more often AF episodes are present, the more pronounced atrial remodeling and vulnerability for further AF development become (“AF begets AF”) (889).

Remodeling in AF is a complex and still not fully elucidated process (7, 30, 34, 887, 890–892). The most well-established phenomenon in AF is downregulation of L-type I_{Ca} and the corresponding mRNA and proteins. This occurs irrespective of the underlying cause of AF and is observed in AF both with and without heart failure. It is

considered to be the main cause of APD shortening in chronic AF. Also, the upregulation of $K_{ir2.1}$ (the main channel protein of I_{K1}) and TASK-1 channels has been reported to contribute to atrial APD shortening in AF (205). The overall $I_{K,ACH}$ channel ($K_{ir3.1/3.4} + GIRK$) expression is not significantly changed in chronic AF (871), but a constitutively active component of this current that is very weak in sinus rhythm is greatly enhanced (358) and is assumed to shorten the APD in AF. A very recent study also indicated that cholinergic M_1 receptors were upregulated, further activating $I_{K,ACH}$ and thereby shortening atrial repolarization (871). Both downregulation (549, 870) and no change of I_{Kur} have been observed in chronic AF. A recent study in a tachypaced dog AF model (562) confirmed the expression changes of SK2 or SK3 channels, which supported the results of an earlier study (872) in mice. I_{to} is downregulated in chronic AF (7, 549), which is well reflected in the widening of early atrial repolarization of AF and its increased AP duration at 20% repolarization (APD_{20}). Intracellular Ca^{2+} handling is impaired in chronic AF associated with heart failure (893), as increased open probability of the ryanodine receptor SR channels results in more frequent Ca^{2+} release from the intracellular Ca^{2+} store (681, 824, 887). This may subsequently enhance the frequency of spontaneous depolarization in AF via NCX, possibly contributing to the increased triggered activity in chronic AF (803).

Structural remodeling has been observed in a tachypaced AF goat model (880), which seems even more pronounced in AF associated with heart failure (894). This includes elevated levels of fibrosis (34) and other extracellular matrix components such as myofibroblasts, periostin, matrix metalloproteinases (MMPs), and transforming growth factor $\beta 1$ (TFG- $\beta 1$). Kidney disease (895), inflammation (29), and oxidative stress (896, 897) were also associated with arrhythmogenesis and remodeling in AF. Several reports proved the important role of calmodulin-dependent protein kinase II (CaMKII) in both abnormal Ca^{2+} handling and structural remodeling in AF, suggesting CaMKII inhibition as a promising new strategy to treat AF (573, 898, 899).

7.2. Remodeling in Heart Failure

Sudden cardiac death caused by arrhythmias (900) is responsible for a substantial proportion of the mortality in heart failure. The overwhelming majority of published papers confirmed significant lengthening of repolarization of the ventricular muscle without substantial species differences and regardless of its origin. This is also associated with increased dispersion of repolarization (241), which can be further enhanced by bradycardia-induced AP prolongation often seen in this situation. Enhanced

fibroblast/myofibroblast activity, fibrosis, and altered connexin expression (877, 879) impair impulse conduction (881) and contribute to impulse propagation heterogeneity (901, 902). These changes alone and in combination with heterogeneity of repolarization (25, 903) would result in a favorable substrate for reentry arrhythmias (FIGURE 2). An additional source of proarrhythmic substrate is the high vulnerability of failing hearts to repolarization alternans (846, 904), which appears to result mainly from remodeling of calcium handling. For example, Nivala et al. (905) utilized a detailed model of spatiotemporal calcium handling to investigate the consequences of heart failure remodeling. They have shown complex interactions of disruption of T tubules together with SERCA downregulation to promote increased alternans vulnerability. A different theoretical study also highlighted the importance of SR calcium release dynamics and how their changes in heart failure promote alternans (858).

The ionic mechanisms underlying electrophysiological remodeling in the ventricle include downregulation of $K_v4.3$ channels and I_{to} , K_{ir2} channels and I_{K1} , SK2 channels, K_vLQT1 channels, and I_{Ks} (156–159, 866, 873). Peak I_{Na} can be reduced in failing heart by posttranscriptional reduction and deficient glycosylation of $Na_v1.5$ channel α -subunit (862), and these changes may contribute to slowing of impulse and conduction. In a mouse transverse aortic constriction HF model, $Na_v1.5$ remodeling was observed in subcellular microdomains: $Na_v1.5$ cluster size at the lateral membrane and at the intercalated disk was reduced in failing myocytes, in agreement with reduced peak I_{Na} and impaired transversal and longitudinal conduction in failing myocardium (98). More importantly, late I_{Na} is significantly increased both in an experimental heart failure model (127) and in patients (126); the substantial inward current during the plateau phase causes failure of repolarization and decreases its homogeneity, providing substrate for reentry arrhythmias. In rabbit and human ventricular muscle, downregulation and change of the transmural expression pattern of CFTR Cl^- channels was observed (906) in the hypertrophied heart. Connexin 43 protein downregulation and its lateralization delay impulse conduction and can enhance anisotropic impulse propagation (878), further contributing to substrate generation for arrhythmias.

In addition to remodeling of ionic channels, calcium handling is substantially altered, showing increased SR leak and reduced SR reuptake, resulting in low SR calcium loading and thus diminished calcium transient (802). An additional factor contributing to low SR loading and calcium transient is the increased NCX (907). The alterations of calcium

handling affect the SR-mitochondria cross talk, leading to energy starvation of failing cells, affecting energy-sensitive processes (908). CaMKII signaling is also strongly affected, with relevance for arrhythmia formation (802).

Changes in electrophysiology and calcium handling in heart failure promote ectopic automaticity in the PVs, atria, and ventricle, serving as an important trigger for reentry arrhythmias (788, 790, 875, 909, 910). One type of automaticity may arise from pacemaker-like currents in ventricles. The pacemaker HCN4 and HCN2 channels that carry the I_f inward pacemaker current have been reported to be upregulated in ventricular (788, 789, 875, 876, 911) and atrial (912) tissue of heart failure patients. In contrast, downregulation of I_f in the SAN has also been observed (913). A second type of automaticity may arise from afterdepolarizations resulting from increased calcium leak and subsequent spontaneous SR release, together with the upregulated NCX (907). This increased risk of DADs is further enhanced by the above-mentioned reduction in I_{K1} (291), which makes it easier for the depolarization to reach the threshold of I_{Na} reactivation. More importantly, heart failure alters cellular Ca^{2+} handling (681, 914). Calcium leak from the SR is enhanced, resulting in spontaneous Ca^{2+} release from the SR (802, 824, 915). This transient intracellular Ca^{2+} concentration increase activates the already upregulated (907) forward NCX, leading to arrhythmogenic depolarizations serving as triggers in an environment where the substrate also favors the development of arrhythmias due to heterogeneity of impulse conduction and repolarization. In this process, CaMKII seems to have an important role since its inhibition can have beneficial antiarrhythmic consequences (802).

7.3. Remodeling in Hypertrophic Cardiomyopathy and in Athlete's Heart

Hypertrophic cardiomyopathy (HCM) was first described in 1958 after autopsies on individuals who suffered unexpected sudden cardiac death (916). Since then, HCM has been identified as the most common inherited heart disease, with a prevalence of 1:500 (917), caused by >1,400 known mutations in at least 11 genes (most commonly in β -myosin heavy chain, *MYH7* and myosin binding protein C, *MYBPC3* genes) encoding different sarcomeric and Z-disk proteins (243). The disease is characterized by variable left ventricular hypertrophy and fibrosis (918) and increased incidence of serious ventricular arrhythmias (919, 920). Moreover, HCM is the most common cause of SCD in young persons and competitive athletes under the age of 35 yr (919, 921). The increased propensity for ventricular arrhythmia development in patients with HCM is mainly attributed to

structural left ventricular remodeling (922). Indeed, disorganized myocyte architecture (923), intramyocardial and replacement fibrosis, and collagen deposition in regions with chronic microvascular ischemia (924) can serve as substrates for sustained arrhythmias (925). In addition, the surrounding ischemic myocardium manifests impaired conduction and heterogenous repolarization dispersion in advanced stages of HCM (926). Alternans is another source of proarrhythmic substrate in HCM (927). However, most SCD events occur in HCM patients at early disease progression stages, when left ventricular hypertrophy is the only major structural abnormality (928). Accordingly, several key elements and consequences of electrical remodeling have been identified in cardiomyocytes from HCM patients, including more frequent EAD and DAD formation (160), increased diastolic Ca^{2+} concentration and elevated NCX expression (160), and increased left ventricular *HCN4* expression (792), all capable of providing arrhythmia triggers in HCM (27, 929, 930). In addition, prolongation of the APD (160) and, consequently, QTc lengthening were observed in patients with HCM, which can be caused by the reduced densities of I_{to} and I_{K1} , decreased expressions of *hERG1b* and *KCNQ1*, and increased I_{NaLate} and slower I_{CaL} inactivation kinetics (160, 931) in myocytes from HCM patients. These elements of ionic current remodeling were sufficient to recapitulate increased vulnerability to EADs when incorporated into a ventricular myocyte model (776).

In competitive athletes, chronic endurance training leads to the development of the so-called athlete's heart, characterized by lower resting heart rate due to increased vagal tone (932), I_f downregulation (933), and symmetric cardiac hypertrophy (934). The incidence of sudden cardiac death in top competitive athletes is two to four times higher compared with the age-matched population (935). Interestingly, hypertrophic cardiomyopathy is found in almost 40% of the cases of SCD in athletes (919). The electrophysiological mechanisms underlying SCD in athletes are not known (for a review see Ref. 18); nevertheless, a significantly larger short-term variability of the QT interval was found in professional soccer players, indicating increased repolarization temporal instability (936) that can refer to increased arrhythmia susceptibility in this population (259, 937).

7.4. Remodeling in Diabetes Mellitus

Diabetes mellitus represents a significant burden on health care systems all over the world since its prevalence is continuously increasing. Diabetes mellitus, an endocrine disorder, is characterized by reduced insulin production (type 1) or increased insulin resistance (type 2), with the latter belonging to cardiometabolic disorders

and being responsible for ~90% of diabetes mellitus cases. Cardiac repolarization disturbances like QTc lengthening or increased QT dispersion are associated with the disease, and cardiovascular complications including arrhythmias and sudden death are major causes of mortality and morbidity in diabetes. These complications usually develop slowly over several decades and are associated with cardiomyopathy, ischemia, vascular sclerosis, and neuropathy with complex and not fully understood mechanisms. Here, we briefly summarize those electrophysiological and structural changes that can be attributed directly to diabetes-induced remodeling (938). The majority of the available data regarding electrical remodeling are derived from type 1 diabetes animal models. There, diabetes is induced acutely by alloxan or streptozotocin (raising the question of how well the model corresponds to chronic changes developing slowly over decades in humans). Results in type 1 diabetes animal models include lengthening of ventricular repolarization, attributed to downregulation of I_{to} (868) and I_{Ks} currents. At the level of mRNA and protein, $K_v4.2$, $K_v4.3$, and $minK$ were reduced but $K_v1.4$ and K_vLQT1 did not change or were upregulated. Zhang et al. (869, 939) reported significant lengthening of QTc and downregulation of cardiac HERG channels and I_{Kr} in alloxan-induced type 1 rabbit diabetes; however, the latter results regarding I_{Kr} were not confirmed by other studies in rabbits and dogs (271, 867). In Goto–Kakizaki type 2 diabetic rats, $I_{Ca,L}$ and Ca^{2+} transient did not change compared with those in the control animals but decreased atrial KCNN2 mRNA, $K_{Ca2.2}$ protein levels, and corresponding SK2 current densities were observed (874, 940), with concomitantly enhanced myocardial hypertrophy and extracellular matrix deposition with fibrosis (941). In Zucker rats, another type 2 diabetic model, enhanced fibrosis, Cx43 lateralization, and significant APD prolongation with delayed $I_{Ca,L}$ inactivation (942) were observed (865). Another observation in type 1 and 2 rat diabetes models is the reduced impulse conduction reserve (863, 943). In a recent paper, O-GlcNAcylation and impaired function of $Na_v1.5$ channel (864) and I_{Na} were described, which together with the fibrotic structural changes (944) can also contribute to the arrhythmogenic impulse conduction defects (945).

In addition to changes in ionic channels, calcium handling is also altered. Several experimental studies in both type 1 and 2 diabetes models in rat established increased SR Ca^{2+} leak due to enhanced RyR2 channel activity (946, 947), which, as mentioned above, would be expected to result in DADs and extrasystoles. Accordingly, Yaras et al. (948) showed increases in Ca^{2+} spark frequency in cardiomyocytes from RYR2 and decrease in FKBP12.6 (calstabin) association. Also,

enhanced CaMKII-mediated phosphorylation of RyR2 has been linked to aberrant Ca^{2+} handling in the same animal model (949, 950). Although it is less well established, similar pathophysiological alterations have been observed in type 2 diabetic rats (951, 952). Results obtained from experimental diabetes suggest that the diabetic heart provides favorable substrate and increased propensity of trigger for arrhythmias due to enhanced ectopic activity and both impaired impulse conduction and repolarization, but results are not conclusive. Therefore, further studies with more appropriate experimental diabetes models are needed to better understand the mechanisms of arrhythmias in diabetes mellitus.

7.5. Myocardial Ischemia, Infarction, and Arrhythmias

Myocardial ischemia mostly develops on the basis of coronary artery disease following critical decreases in blood flow in obstructed coronary arteries. Occlusion of coronary arteries induces a chain of events within minutes of the onset of ischemia, leading to altered function of ion channels and concomitant ischemia- and infarction-induced cardiac arrhythmias. The majority of cases where ventricular tachyarrhythmias including ventricular fibrillation lead to sudden cardiac death are clearly associated with coronary artery disease and myocardial infarction (953, 954). Reperfusion of the myocardium is necessary for tissue survival; however, it can also lead to reperfusion-induced arrhythmias (955, 956). When timely revascularization is not performed, coronary obstruction leads to irreversible cell damage termed myocardial infarction, and the dead cardiomyocytes are replaced by scar tissue. The remodeling in surviving epicardial and border zone myocytes mostly leads to conduction abnormalities, while surviving endocardial Purkinje fibers can be important sources of triggered activity (618). In addition, over the course of days and weeks, the noninfarcted myocardium, including the peri-infarct border zone, also undergoes significant remodeling that favors arrhythmia development due to changes in conduction, refractoriness, and triggered activity (31). An additional source of increased dispersion of refractoriness is the vulnerability of the infarct border zone to alternans, shown both computationally (847) and experimentally (847). Such spatially localized alternans is proarrhythmic in a fashion similar to spatially discordant alternans, forming steep gradients of repolarization. Multiple other studies have investigated arrhythmia mechanisms associated with myocardial ischemia and infarction; for comprehensive detailed reviews, the reader is referred to works by Janse and Wit (31) and Pinto and Boyden (784).

In the acute phase of myocardial ischemia (within minutes to 2–4 h after coronary blood flow reduction), ventricular arrhythmias including fibrillation occur in humans (957) and also in experimental animals subjected to complete coronary artery occlusion (958, 959).

Acute ischemia promotes the formation of arrhythmia substrate, which allows reentry via several mechanisms. The resting membrane potential of ischemic cardiomyocytes is significantly depolarized (960), partly due to marked K^+ loss and intracellular acidosis (783), leading to extracellular K^+ accumulation in ischemic tissue (961). The depolarization of the resting membrane potential depresses action potential upstroke and amplitude by reducing I_{Na} and results in the prolongation of the refractory period via slow recovery from inactivation of the sodium gates (39). Activation of ATP-dependent potassium channels shortens the action potential duration (962). Within 15 min of the onset of ischemia, gap junction channel phosphorylation status is changed and they get translocated into intracellular pools in ischemic cells (963), severely reducing cell-to-cell coupling (815, 964, 965). These changes result in impaired impulse conduction in acute ischemia (966). Increased spatial dispersion of repolarization and refractoriness between different regions of the myocardium is also an important arrhythmia substrate (128). Nonuniform shortening of the action potential due to heterogeneous sarcolemmal $I_{K,ATP}$ activation in myocytes from the ischemic and border zone (reviewed in Ref. 967) and no shortening of AP in the normoxic myocardium increases dispersion of repolarization and effective refractory period within minutes after ischemia onset (340). The first phase of ventricular arrhythmias (“phase 1a”) peaking between 5 and 6 min after the onset of ischemia in experimental models is usually, but not exclusively, attributed to the mechanisms described above (31, 968), which have been further investigated in computer simulation studies using human biventricular models (969).

Multiple mechanisms underlie the formation of arrhythmia triggers in acute ischemia. The increased release of catecholamines occurs 15–20 min after the onset of myocardial ischemia (970), possibly increasing ectopic activity. Early and delayed afterdepolarizations can supply the triggers for arrhythmia initiation in acute myocardial ischemia. Early afterdepolarizations can develop in Purkinje fibers in acute ischemia because of intracellular acidosis and exposure to ischemia-induced release of lysophosphatidylcholine (971). Delayed afterdepolarizations can occur in ischemic cells because of acidosis, hypoxia, and calcium overload (617). A so-called “injury current” flowing from ischemic myocardium to normal myocardium can cause increased abnormal automaticity in acute myocardial ischemia. The basis for this current is the difference in membrane

potentials between neighboring ischemic (depolarized) and normoxic (hyperpolarized) myocardium and has been shown to contribute to ectopic activity in experimental conditions (972–974) and computer simulations (706). In general, the initiation of so-called “phase 1b” arrhythmias in experimental models of myocardial ischemia is mostly attributed to increased automaticity (31).

In the subacute and chronic phases of myocardial infarction, reentry and triggered activity caused by early and delayed afterdepolarizations are major mechanisms of infarction-induced ventricular arrhythmias (28, 975), where surviving Purkinje fibers (976) and epicardial border zone myocytes (977) play a critical role in arrhythmia development. A series of papers by the Boyden group describe the morphological and electrophysiological changes occurring over 24–48 h after an infarction in surviving left ventricular Purkinje cells that underlie subacute spontaneous arrhythmias (for a detailed review, see Ref. 784). In general, surviving Purkinje fibers exhibit depolarized resting potentials associated with reduced I_{K1} (978), decreased $I_{Ca,L}$ and $I_{Ca,T}$ densities (979), prolonged repolarization with up to 51% smaller I_{to} density, and delayed I_{to} reactivation kinetics (980). Also observed were nonuniform calcium transients and abnormal calcium waves leading to spontaneous action potentials and triggered activity in the infarcted heart (619). The surviving epicardial myocytes of the border zone next to the infarcted area exhibit decreased excitability and resting potential, reduced upstroke velocity and amplitude of the action potential (977), and, importantly, marked postrepolarization refractoriness (32, 981) due to decreased I_{Na} density and altered I_{Na} kinetics (982). A pathological redistribution of connexin 43 gap junction protein and reduced gap junctional conductance was observed in border zone surviving cardiomyocytes (983). These changes lead to abnormal, slow, and anisotropic impulse conduction (28, 984, 985). Interestingly, in these surviving epicardial myocytes, a gradual shortening and triangularization of the action potential was observed over 2 wk, followed by a return of action potential parameters to normal by 2 mo after myocardial infarction (986). The reduced $I_{Ca,L}$ density (987) may be partly responsible for the triangularization of the action potentials on these cells. Several important repolarizing K^+ currents are downregulated in surviving epicardial cells, including I_{to} (977) and I_{Kr} and I_{Ks} (240), leading to prolonged action potentials. These changes described above in epicardial border zone myocytes strongly favor the development of reentry and, of particular interest, anisotropic reentry (7).

In addition to the changes described above, the remote noninfarcted regions of the myocardium also

exhibit structural and electrical remodeling as the remaining myocardium in the infarcted heart adapts to increased workload (988). The developing regional left ventricular hypertrophy is an important risk factor for the generation of severe ventricular arrhythmias (989) and probably relates to enhanced dispersion of repolarization associated with myocardial hypertrophy.

7.6. Aging-Associated Cardiac Remodeling

There is a dramatic increase in the incidence and prevalence of cardiovascular disease and mortality with age, and aging is now identified as a major risk factor for cardiovascular morbidity (990). Evidence suggests that cardiovascular aging is associated with remodeling of the heart, setting the stage for arrhythmia development (especially atrial fibrillation and ventricular tachycardia) and reduced cardiac function. The incidence of sudden cardiac death increases with age (991); however, our understanding of the mechanisms responsible for increased incidence of arrhythmias in the elderly remains limited (992). Many of the aging-associated alterations are, at least in part, inevitably due to the observed coronary artery dysfunction, increased artery stiffness, decreased responsiveness to β -adrenergic stimulation, and cardiac extracellular matrix remodeling found in the elderly (993–995).

The pacemaker function of the sinus node significantly decreases in older patients, probably because of replacement of pacemaker cells within the sinoatrial node (SAN) by extracellular matrix (996). Animal studies suggest that decreased expression of HCN2, $I_{Ca,L}$, $I_{Ca,T}$, and $K_v1.5$ channels can also contribute (548, 997, 998). Consequently, the rate of spontaneous diastolic depolarization falls and action potential duration is prolonged in pacemaker cells (523, 999). The intrinsic heart rate decreases (997), with concomitant fatigue, bradycardia, and increased incidence of supraventricular arrhythmias including atrial fibrillation in the elderly (1000).

The observed delayed and impaired cardiac impulse conduction, with concomitant QRS complex widening, is the result of decreased Cx43 expression and degenerative changes in the cardiac connective tissue (992, 1001–1003).

In aged ventricles, even without the presence of structural heart disease, loss of cardiomyocytes, reactive hypertrophy in the left ventricle, fibrosis, and changes in repolarization occur (161, 1004–1006). The prolongation of the ventricular action potential was observed in senescent sheep (1007), and consequent QT interval lengthening was shown in old dogs (1007, 1008). In an attempt to maintain cardiac function, ion channel remodeling involving $I_{Ca,L}$, I_{to} , K_{ATP} expression changes, delayed $I_{Ca,L}$ inactivation, and increased $I_{Na,late}$ are probably

responsible for repolarization prolongation in aged hearts (1009, 1010). These elements of ventricular remodeling in the aged heart increase susceptibility toward arrhythmias by altering cellular coupling, increasing anisotropic conduction, and enhancing heterogeneity of refractoriness in the myocardium, which are changes that all together favor reentry initiation and stabilization. The increased expression of NCX, the delayed inactivation of $I_{Ca,L}$, together with reduced expression of SERCA and other proteins related to calcium handling all contribute to impaired calcium homeostasis and provide the mechanisms for increased triggered activity in the aging myocardium (1011–1015).

The ability of the heart to properly respond to autonomic stimuli also decreases with aging (1016). Reduced β -adrenoceptor responses and receptor densities were identified in the aging myocardium (1017, 1018), exacerbated by decreased cAMP production (995). It is not clear how impaired cAMP-dependent regulation of I_{Ks} (1019) and $I_{Ca,L}$ (1020) translates into alterations of repolarization reserve in the elderly. In addition, decreased vagal component of heart rate variability and heart rate responses were observed after muscarinic acetylcholine receptor blockade (1021, 1022). The impaired autonomic regulation of the heart and the electrical and structural remodeling described above in the elderly contribute to reduced cardiac adaptive responses and increased supraventricular and ventricular arrhythmia susceptibility (1023).

8. INHERITED CONDITIONS ASSOCIATED WITH ION CHANNEL DYSFUNCTION

Cardiac arrhythmias are usually symptoms or consequences of other underlying diseases such as myocardial ischemia or infarction, heart failure, hypertension, diabetes, etc. However, cardiac ion channel mutations or polymorphisms (1024) can represent the primary cause of arrhythmias, collectively called “ion channelopathies” (1025). This field is particularly rapidly expanding, and detailed discussion is far beyond the scope of this review; some excellent recent reviews are suggested for further reading (114–117, 149, 246, 1026–1029).

In general, mutation of a certain ion channel can cause gain or loss of function (1029–1032) resulting in increased or decreased current through the affected ion channel, which may alter arrhythmia trigger and/or substrate (TABLE 1) (245, 1033, 1034).

Congenital LQT syndrome is characterized by prolongation of myocardial AP and QT interval caused by the reduction of repolarizing current due to either loss-of-function mutations in repolarizing current-conducting potassium channels or gain-of-function mutations in

depolarizing current-conducting sodium or calcium channels (114, 115) (TABLE 1). Congenital LQT syndrome is commonly associated with the development of TdP and sudden cardiac death (1035), and most LQT syndrome subtypes show an autosomal dominant inheritance (115). In >90% of patients with congenital LQT, genetic variants of *KCNQ1* encoding the α -subunit $K_v7.1$ of I_{Ks} (LQT1; 30–35% of cases), *KCNH2* encoding the α -subunit $K_v11.1$ of I_{Kr} (LQT2; 25–40% of cases), and *SCN5A* encoding the α -subunit $Na_v1.5$ for I_{Na} (LQT3; 5–10% of cases) underlie the disorder (122, 1036, 1037) (TABLE 1). A number of other genes encoding ion channel proteins or their regulators have been implicated as causes of congenital LQT syndrome (TABLE 1). For details on the causative roles of the genetic variants involved in the different congenital LQT syndrome subtypes, the reader is referred to other comprehensive reviews (115, 246). In LQT syndrome, prolongation of repolarization and refractoriness, accompanied with increased dispersion of repolarization (1038, 1039), enhance the substrate for typical ventricular arrhythmias in patients with LQT syndrome such as TdP polymorphic tachycardia and ventricular fibrillation. Enhanced triggered activity due to early afterdepolarizations, elicited by reactivation of I_{CaL} during the prolonged AP, provides the trigger for the development of TdP in LQT syndrome (796, 1038). LQT syndrome is characterized by incomplete penetrance and can be “silent,” i.e., no significant prolongation of repolarization and QT interval is observed. However, congenital LQT syndrome greatly enhances the effect of any other factor which delays repolarization by other mechanisms. This can be explained by the concept of “repolarization reserve,” as introduced in sect. 3.4.2 (228, 257, 1040, 1041). Accordingly, impaired function of different types of potassium channels (caused by genetic mutation, disease-induced downregulation, or drug effects) can add together, further enhancing the substrate for ventricular arrhythmias. Of note, ion channel polymorphisms can also play a role in arrhythmia development, thus emphasizing the importance of pharmacogenetics during the evaluation of proarrhythmic drug-induced adverse effects (798, 1024). Which current is affected by such polymorphisms (usually potassium currents, I_{CaL} , or I_{NaLate}), may largely determine the individual’s response to antiarrhythmic channel-blocking drugs, emphasizing the concept of personalized medicine.

SQT syndrome (1042, 1043) is a rare, albeit severe, channelopathy that is characterized by abnormally short frequency-corrected QT intervals (<360 ms), due to accelerated ventricular repolarization (1044), with a high risk of sudden cardiac death and AF (1045). SQT syndrome shows autosomal dominant inheritance, and gain-of-function mutations in genes encoding different potassium

channels, i.e., *KCNH2* (SQT1), *KCNQ1* (SQT2), and *KCNJ2* (SQT3), have been associated with the disorder (1046–1048) (TABLE 1). In addition, loss-of-function mutations in genes encoding voltage-gated calcium channel subunits *CACNA1C*, *CACNB2b*, and *CACNA2D1* were designated as SQT4, SQT5, and SQT6, respectively (1049) (TABLE 1). Patients with SQT syndrome involving calcium channel mutations exhibit an overlapping phenotype combining short QT and a Brugada syndrome phenotype (1050). Loss-of-function mutations in the gene (*SLC22A5*) encoding a sodium-dependent carnitine transporter have been termed SQT7 (1051) (TABLE 1). In SQT7, the mechanistic link between short QT and carnitine concentrations remains elusive; however, increased I_{Kr} due to the lack of long-chain acylcarnitines may play a role (1052). SQT8 syndrome involves a mutation in the gene (*SLC4A3*) encoding a Cl^-/HCO_3^- exchanger (AE3) leading to a trafficking defect of the mutated AE3 to the cell membrane (1053) (TABLE 1). The shortening of APD and ERP in the myocardium, as well as the increased spatial dispersion of repolarization, due to more enhanced APD shortening in the epicardium, all favor reentry tachycardia development both in the ventricles and in the atria in SQT syndrome (1054, 1055).

Brugada syndrome (BrS) (1056) and arrhythmogenic right ventricular cardiomyopathy (ARVC) (1057) are inherited cardiac diseases with a complex genetic background. Brugada syndrome is characterized by ST segment elevation in right precordial leads and has been considered as the cause of SCD in up to 20% of patients with a structurally normal heart (778). Approximately 20–30% of patients with BrS exhibit pathogenic mutations in the *SCN5A* gene encoding the α pore-forming subunit of the cardiac $Na_v1.5$ sodium channel (1058), leading to loss of function in fast I_{Na} and, consequently, conduction slowing and delayed right ventricular activation (1059, 1060). In BrS, because of decreased I_{Na} the balance of outward and inward currents changes and the repolarizing effect of I_{to} is amplified in epicardial but not in endocardial cells, resulting in enhanced transmural dispersion of repolarization. This increased dispersion can create a vulnerable window for extrasystoles to induce phase 2 reentry arrhythmias (1061, 1062). In a genome-wide association study, genetic variants of *SCN10A*-encoded $Na_v1.8$ sodium channels, playing a key role in cardiac neurons (1063) but also expressed in the working myocardium (1064), have been identified as strong modulators for BrS (1065). In addition, in ~2–5% of BrS patients pathogenic variants have been identified in a number of genes encoding other ion channel proteins, and up to 70% of patients with BrS have an unidentified genetic cause (778, 1058). Interestingly, the expression of $K_v4.3$, a key subunit of I_{to} (135), was markedly reduced in the endocardium but not in the epicardium in patients with BrS (1066). This enhanced transmural difference in

I_{to} can lead to increased transmural dispersion of repolarization in BrS patients, favoring the development of reentry arrhythmias (24, 1062).

In patients with ARVC, a significant number of cardiomyocytes in patches of the right ventricular free wall are replaced by fibroadipose tissue, with marked pathological consequences for myocardial depolarization and repolarization of the right ventricle (1057). The causative role of mutations in at least 16 genes, mostly encoding different desmosomal proteins, has been identified in ARVC (1067), whereas in 40–50% of patients the genetic cause is unknown (1068). The exact molecular mechanisms for how desmosome assembly impairment and dysfunction lead to cardiomyocyte apoptosis and their fibroadipose replacement are not fully understood (1069, 1070). ARVC is associated with frequent ventricular extrasystoles, ventricular tachycardia with left bundle branch block morphology, syncope, and SCD (1071). On autopsy, ARVC is found to be responsible for SCD in 5% of young competitive athletes in the United States, whereas this number is around 27% in northern Italy (1072, 1073). The fibroadipose tissue patches correspond to electroanatomical scars that promote the establishment of scar-related macro reentry circuits (1074, 1075).

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by a normal resting ECG; however, malignant ventricular arrhythmias and SCD are induced by adrenergic stimulation (821, 1076). Mutations in *RYR2*, encoding the ryanodine receptor 2, the Ca^{2+} release channel located on the SR (autosomal dominant CPVT type 1), and in *CASQ2*, encoding calsequestrin 2, the calcium binding protein inside the SR (autosomal recessive CPVT type 2), makes these channels and calcium storage sites more sensitive to catecholamine-induced Ca^{2+} release (1077). Consequently, spontaneous triggered automaticity is induced by depolarizations due to increased transient inward current elicited by forward NCX activity during diastole. Iyer et al. (1078) used computer simulations to characterize the impact of *RYR2* and calsequestrin mutations in the CPVT phenotype. Their study shows how impaired SR calcium sensing and increased spontaneous SR calcium release promote DADs and how these events are aggravated by β -adrenergic stimulation.

Mutations in I_f pacemaker channels can cause both brady- and tachycardias (1034) by altering sinus automaticity. Sinus bradycardia was also reported in patients with loss-of-function mutation of the *SCN5A* sodium channels resulting in failure of pacemaker capture (1079). Some familial AF cases are also linked to different ion channel mutations in the atria, influencing repolarization, depolarization, connexin function, and consequently impulse conduction properties (1080).

9. OTHER FACTORS INFLUENCING ARRHYTHMOGENESIS

9.1. Sex Differences in Cardiac Electrophysiology and Arrhythmias

Sex differences in cardiac electrophysiology carry marked clinical significance because they translate into distinct arrhythmia risks and outcome in men and women. Although women have a somewhat smaller risk of AF or ventricular fibrillation (VF) compared with men (1081), this does not hold for all causes of arrhythmia. For example, women have a longer frequency-corrected QT interval and are more susceptible to development of drug-induced polymorphic ventricular tachycardia (1082–1085), whereas men are more likely to exhibit early repolarization (150). Here we briefly discuss the underlying mechanisms for sex differences in cardiac electrophysiology; for more detailed discussions the reader is directed to recent comprehensive reviews (265, 1081).

Sex hormones exert their effects via both transcriptional regulation (1086, 1087) and acute, nongenomic modulation of intracellular signaling (1088). Women exhibit greater sinoatrial node automaticity (1089), and pregnancy increases pacemaker I_f current density along with HCN2 expression in mice (1090). A larger I_{NaLate} was observed in male rabbit left atrial posterior wall myocytes (1091). Since these cells are major sources of non-pulmonary vein triggered activity (204, 1092), and I_{NaLate} is an important contributor in atrial arrhythmogenesis (1093), the larger I_{NaLate} may contribute to higher triggered activity in males, leading to the initiation of AF.

The prolonged ventricular repolarization in women is partly due to decreased expression of pore-forming and/or auxiliary subunits of ion channels carrying repolarizing currents, including I_{to} , I_{K1} , I_{Kr} , I_{Ks} , and K_{ATP} in humans (151), and these results are generally in agreement with animal studies showing lower densities for these currents (263, 1094–1096). In addition, 17β -estradiol (E_2) directly (nongenomic effect) reduces I_{Kr} and enhances I_{Kr} block and QTc prolongation by HERG blocker drugs (1085, 1097), whereas testosterone increases I_{Kr} and I_{Ks} (1094, 1098) and progesterone enhances I_{Ks} (1099). Indeed, the normalization of the QTc interval in a woman with long QT syndrome was observed during pregnancy due to increased progesterone levels (1100). A greater transmural I_{Ks} density gradient was found in female dogs compared with males (1101), possibly contributing to larger transmural APD heterogeneity in females. Opposite effects of β -adrenergic stimulation by isoproterenol on Purkinje fiber APD were observed in male dogs (APD shortening) compared with female dogs (APD prolongation), highlighting sex- and age-related differences in the autonomic regulation of

the cAMP-dependent I_{Ks} current (1102, 1103). Since I_{Ks} is a key current for repolarization reserve (228, 250, 260), these changes may lead to reduced repolarization reserve and an increased arrhythmia substrate in women.

A more heterogeneous transmural I_{Na} distribution was found in female canine left ventricle (1104), and testosterone increased epicardial I_{Na} amplitude in female dogs to levels similar to those measured in male epicardium (1104). As I_{Na} and I_{to} have opposing effects on repolarization, increased transmural heterogeneity in ion channel expression creates transmural dispersion of repolarization that serves as an arrhythmogenic substrate (128). Sex-dependent differences in $I_{Ca,L}$ densities and Ca^{2+} homeostasis protein expression and regulation (162) lead to sex differences in triggered activity, since the reactivation of the L-type calcium current during the plateau of the action potential and Ca^{2+} cycling protein dysfunction importantly contribute to EAD formation (10). Larger $I_{Ca,L}$ densities were found in all transmural layers of the left ventricle in female dogs (1101), possibly contributing to a bigger transmural heterogeneity of APD in females, since I_{Ks} (similar in male and female midmyocardium) could not offset the increased $I_{Ca,L}$. In addition, estradiol increased $I_{Ca,L}$ (1105) and promoted EAD formation and sudden cardiac death in rabbits with LQT2 syndrome (1106), whereas testosterone and progesterone exerted opposite effects (1088, 1106, 1107). In female rabbit left ventricle, NCX expression and current were higher, resulting in increased EAD development following the administration of the HERG blocker dofetilide (1108). Testosterone, however, increased SERCA function, causing rapid removal of excess intracellular Ca^{2+} (1109). Testosterone increased RyR2 activity (1109), whereas estradiol increased RyR2 leakiness and contributed to the formation of proarrhythmic afterdepolarizations (1110). A significantly lower expression of Cx43 was found in left ventricular myocardium in women compared with men (151) that can make women more susceptible to ventricular conduction impairment.

In summary, sex hormones significantly modulate both the arrhythmia substrate and triggered activity leading to sex differences in ECG morphology and susceptibility to supraventricular and ventricular arrhythmias. Estradiol lengthens repolarization, promotes EAD formation, and exacerbates the QT-prolonging effect of HERG blocker drugs, leading to higher incidence of cardiac arrhythmias in females, whereas testosterone and progesterone exert mostly opposite effects.

9.2. Serum Ion Concentration Changes

Potassium is by far the most important ion in blood that affects arrhythmogenesis (233, 1111–1113). As mentioned

above, extracellular K^+ concentration significantly modulates several K^+ currents (225, 233–235, 294, 1114) in the range of blood K^+ concentrations (2–10 mM) observed frequently in clinical practice. Hyperkalemia depolarizes the cell, as expected from the Nernst equation. The depolarization caused by elevated extracellular $[K^+]_o$ can also slow impulse conduction indirectly, by decreasing I_{K1} and partially inactivating inward currents. This happens during ischemia and when K^+ accumulation occurs in the intercellular clefts, not immediately handled by the Na^+-K^+ pump. This latter mechanism may contribute to frequency-dependent regulation of APD and conduction as well (4). I_{Kr} is increased by elevation of extracellular K^+ concentration and decreased in hypokalemia (235, 294, 1115), which is not what would be expected from its transmembrane concentration gradient and is explained by hypokalemia-induced acceleration of rapid I_{Kr} inactivation (225). This may have a role in frequency-dependent APD regulation, and it helps in understanding why hypokalemia enhances the risk of arrhythmias by causing prolongation of repolarization at slow heart rate. I_{Ks} , unlike I_{Kr} , is reduced by elevated $[K^+]_o$ and increased by hypokalemia (235, 294). Therefore, I_{Ks} may serve as part of the repolarization reserve in hypokalemic patients. Hypokalemia and diminished I_{K1} can decrease background K^+ currents, which may favor ectopic automaticity not counterbalancing existing inward currents such as I_f or NCX and may act as enhanced triggers for arrhythmia development. Hypokalemia was shown to decrease Na^+-K^+ pump activity, thereby elevating intracellular $[Na^+]_i$ and leading to increased DAD formation via enhanced NCX function (1116). Hypokalemia also decreases I_{Kr} and consequently prolongs repolarization (225, 235, 1117), decreases repolarization reserve, and often leads to torsade de pointes tachycardia, especially when K^+ channels are already inhibited by concomitant drug therapy. Hypomagnesemia has a similar effect but with a different mechanism. The Mg^{2+} ion acts as endogenous Ca^{2+} antagonist, and in the case where its serum level is low it cannot fine-tune the influence of $I_{Ca,L}$ in sinus node function, repolarization, and possible EAD and DAD formation (1118).

9.3. Proarrhythmic Drug Effects

Not only can diseases, remodeling, serum electrolyte disturbances, and genetic disorders contribute to arrhythmogenesis, but so can drugs, i.e., they may possess proarrhythmic actions. Positive inotropic drugs like digitalis, which inhibits the Na^+-K^+ pump and enhances Ca^{2+} release of SR, can cause DADs, whereas phosphodiesterase inhibitors like milrinone or sympathetic stimulators (1119) like amphetamine, epinephrine, and norepinephrine increase intracellular cAMP levels (1120,

1121), and they consequently increase I_f -related and Ca^{2+} overload-induced automaticity; all of these represent enhanced triggers for arrhythmias. A large number of drugs inhibit I_{Na} and impulse conduction including class I antiarrhythmic drugs like quinidine, flecainide, propafenone, and tricyclic antidepressants (202, 1122, 1123). These drugs, despite the fact that some of them are used to abolish arrhythmias, can also elicit ventricular tachyarrhythmia (1124, 1125), presumably by converting areas in damaged tissue into areas with unidirectional impulse conduction block, which is one prerequisite of reentry arrhythmias, i.e., enhancing the substrate for arrhythmogenesis.

Another proarrhythmic drug effect is prolongation of ventricular repolarization (1126). This proarrhythmic mechanism, which was discussed above, can enhance both the arrhythmic triggers by inducing EADs and the substrate by enhancing dispersion of repolarization. A constantly growing number of drugs have such effects, such as class III antiarrhythmics like sotalol and ibutilide, antibiotics like erythromycin, antihistamines like terfenadine and astemizole, antidepressants like sertindole, and antimalarial drugs like dihydroartemisinin and piperazine (1127). Most of these drugs had been identified to inhibit I_{Kr} or HERG current; therefore, the assessment of HERG current-blocking properties of drug candidates became mandatory in cardiac safety testing in drug development (1128). It must be emphasized that some drugs can induce repolarization abnormality-related arrhythmias without apparent repolarization prolongation by impairing repolarization reserve (260). Therefore, drug effects on other repolarizing currents such as I_{Ks} , I_{K1} , and I_{to} should also be considered to avoid possible proarrhythmic complications of novel compounds in development. Computer simulation studies have recently demonstrated the importance of evaluating multichannel effects for the prediction of drug-induced arrhythmic risk (715).

For a more detailed overview of proarrhythmic adverse effects of drugs, we refer the reader to Refs. 108, 597, 1129–1132.

10. CONCLUSIONS

Cardiac arrhythmias such as VF, TdP, and AF still threaten the lives of millions of patients worldwide. Although the underlying causes of arrhythmia development are variable, including ischemia, heart failure, HCM, diabetes, extreme endurance training, or genetic causes, the direct mechanisms leading to these arrhythmias depend on changes of cellular electrophysiological properties or function of the heart. Therefore, to prevent or treat cardiac arrhythmias, and their most serious consequences, sudden cardiac death and stroke, improved

management and prevention of underlying diseases are needed. This requires a better understanding of the cardiac electrophysiological function and how it may be modulated. The latter includes the improved understanding of the nature of cardiac action potentials in various regions of the heart and the function of the underlying transmembrane ionic currents, pumps, and the development of novel techniques and tools like *in silico* modeling. Pathophysiological changes in the expression and function of transmembrane currents and pumps lead to disturbances of impulse formation, conduction, and refractoriness of cardiac muscle. These would favor the onset of “triggers” and providing the “substrate” for these arrhythmias to develop. Therefore, further intensive research is required to improve our understanding of the physiology, pathophysiology, and genetic and hormonal modulation of these ion channels and pumps in order to develop more efficacious treatment modalities, thereby saving millions of lives in the future.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.V., N.N., L.V., B.R., and I.B. prepared figures; A.V., J.T., N.N., E.P., B.R., and I.B. drafted manuscript; A.V., J.T., N.N., L.V., E.P.,

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