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Review

Remodelling of cardiac repolarization: how homeostatic responses can lead to arrhythmogenesis

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Cardiac action potentials (APs) are driven by ionic currents flowing through specific channels and exchangers across cardiomyocyte membranes. Once initiated by rapid Na^+ entry during phase 0, the AP time course is determined by the balance between inward depolarizing currents, carried mainly by Na^+ and Ca^{2+}, and outward repolarizing currents carried mainly by K^+. K^+ currents play a major role in repolarization. The loss of a K^+ current can impair repolarization, but there is a redundancy of K^+ currents so that when one K^+ current is dysfunctional, other K^+ currents increase to compensate, a phenomenon called 'repolarization reserve'. Repolarization reserve protects repolarization under conditions that increase inward current or reduce outward current, threatening the balance that governs AP duration. This protection comes at the expense of reduced repolarization reserve, potentially resulting in unexpectedly large AP prolongation and arrhythmogenesis, when an additional repolarization-suppressing intervention is superimposed. The critical role of appropriate repolarization is such that cardiac rhythm stability can be impaired with either abnormally slow or excessively rapid repolarization. In cardiac disease states such as heart failure and atrial fibrillation (AF), changes in ion channel properties appear as part of an adaptive response to maintain function in the face of disease-related stress on the cardiovascular system. However, if the stress is maintained the adaptive ion channel changes may themselves lead to dysfunction, in particular cardiac arrhythmias. The present article reviews ionic remodelling of cardiac repolarization, and focuses on how potentially adaptive repolarization changes with congestive heart failure and AF can have arrhythmogenic consequences.

1. Cardiac repolarization

Repolarization refers to the series of transmembrane voltage changes that return cardiomyocytes to their maximally polarized (resting) state following action potential (AP) activation. The repolarization process requires that outward currents, carried predominantly by K^+ (making the cell more negative intracellularly), exceed inward currents carried by Na^+ and Ca^{2+} (which make the cell more positive intracellularly), as illustrated in *Figure 1A*. *Figure 1B* depicts AP characteristics in different regions of the heart. In so-called 'fast-channel tissues', including the working myocardium (atria and ventricles) and Purkinje fibres, the AP exhibits a negative resting membrane potential (~ -80 mV) determined by the large resting K^+-conductance, due to high resting inward-rectifier K^+ current (I_{K1}) permeability. In these regions, the AP displays rapid initial depolarization (phase 0) due to fast inward flow of Na^+ current (I_{Na}) through voltage-gated Na^+ channels. Following a rapid but transient early repolarization phase (phase 1), there is a relatively positive plateau phase (phase 2), lasting over a 100 ms, during which inward currents, such as small components of I_{Na} and in particular the L-type Ca^{2+} current (I_{CaL}), balance outward currents. The plateau is terminated by phase 3 repolarization, due to an increase in several K^+ currents of which the rapid delayed-rectifier I_{Kr} is the most important. Finally, I_{K1} returns the membrane back to the resting potential (phase 4).[1,2] Tissues with spontaneous automaticity can act as pacemakers because they exhibit gradual phase 4 depolarization, due largely to a relatively non-selective 'funny' current, I_f. Changes in the repolarization process can have a major impact on duration and shape properties of fast-channel APs, which are key determinants of several important cellular functions, including contraction and refractoriness. Sinoatrial and atrioventricular node cell APs have a resting K^+ conductance that is smaller (typically ~ -50 to -60 mV), because of a negligible I_{K1}, compared with fast-channel tissue.[2] Nodal APs lack a plateau phase, have slow I_{CaL}-mediated phase 0 depolarization and show

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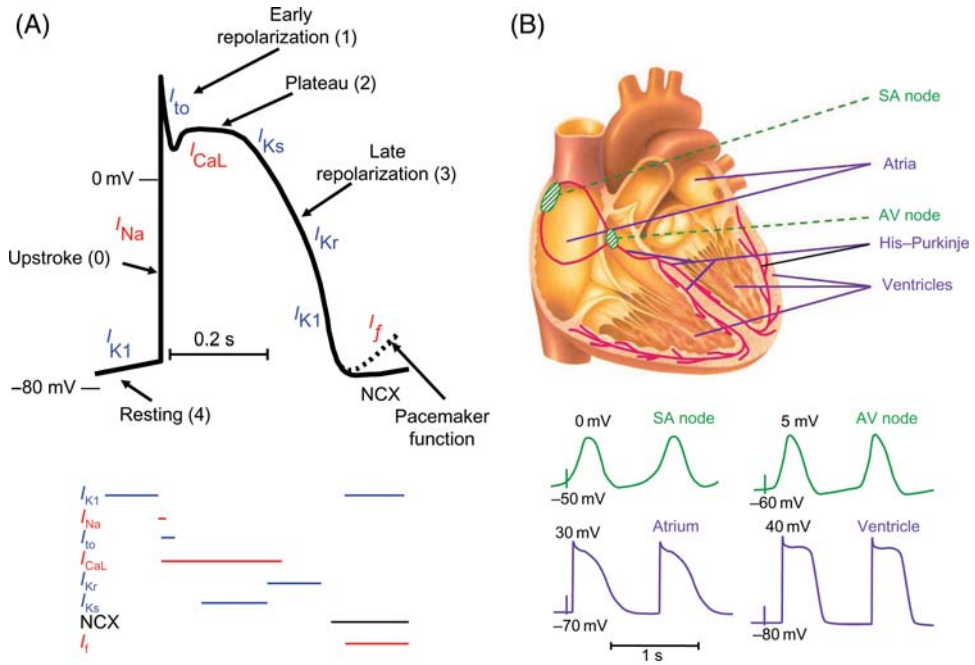

Figure 1 (*A*) Schematic cardiac action potential (AP) with phases and principal corresponding ion currents indicated. Red, inward (depolarizing) current; blue, outward (repolarizing) current. Horizontal lines at the bottom indicate the portions of the AP during which each current flows. I_{K1}, inward-rectifier background K^+ current; I_{Na}, Na^+ current; I_{to}, transient-outward K^+ current; I_{Ks}, slow delayed-rectifier K^+ current; I_{Kr}, rapid delayed-rectifier K^+ current; I_f, 'funny' current (sometimes called 'pacemaker current' because of its apparently important role in cardiac pacemaker function). (*B*) Various specialized tissues in the heart and typical corresponding APs. The short vertical lines indicate the time of onset of activity in the SA node for one beat. Green, slow-channel tissue (nodes); violet, fast-channel tissues.

more gradual repolarization than working myocardial or His–Purkinje system cells.

2. Repolarization reserve

Repolarization reserve was first described by Roden in 1998 to explain variability in drug-induced torsade de pointes (TdP) occurrence.[3] Normal hearts show spare repolarizing capacity because several K^+ currents with different properties are available to contribute outward current. When one current is reduced through drug actions, an ion-channel mutation or acquired diseases, others can increase and compensate. This compensation may result from functional enhancement of a K^+ current related to AP prolongation,[3] or from increased expression of a K^+ current.[4] However, excessive reduction in one current, or blockade of more than one current, may compromise 'repolarization reserve' and lead to arrhythmias.

3. Remodelling of cardiac repolarization during congestive heart failure

Congestive heart failure (CHF) is a major cause of death worldwide. Approximately half of the CHF mortality rate is due to sudden cardiac death, often caused by ventricular tachyarrhythmias.[5] Prolongation of ventricular AP duration (APD), reflecting impaired repolarization, is a consistent finding in patients with CHF and in animal models.[6–8] There is evidence that ventricular APD prolongation maintains Ca^{2+} transients and contractility in the failing heart,[9] and improves mechanical efficiency.[6] It is therefore tempting to speculate that repolarization changes result from an attempt of the cell to maintain cell Ca^{2+} and contractility as the CHF syndrome develops (*Figure* 2). CHF also activates neurohumoral (sympathetic and renin–angiotensin) systems designed to restore blood pressure, increase heart rate, increase cardiac output and improve cardiac contractility. However, when maintained for prolonged periods these homeostatic responses can produce major disturbances in cardiomyocyte function and remodelling of ion currents, further contributing to repolarization abnormalities.

3.1 Ionic basis for repolarization remodelling in congestive heart failure

A variety of inward current alterations occurring in CHF can affect repolarization. Late I_{Na} ($I_{Na,late}$) due to slowly inactivating Na^+ current is increased,[10] contributing to APD prolongation.[11] I_{CaL} remains largely unaltered in failing human hearts or experimental CHF-animal hearts,[7,12,13] but reduced I_{CaL} has also been reported in some studies.[14] Cellular Ca^{2+} handling is importantly altered in CHF. Sarcoplasmic reticulum (SR) Ca^{2+} stores are reduced, SR Ca^{2+}-ATPase (SERCA, the principal SR Ca^{2+} uptake mechanism) is downregulated, relaxation of the systolic Ca^{2+} transient is slowed and diastolic Ca^{2+} may be increased.[15] The Na^+–Ca^{2+} exchanger (NCX) is an electrogenic ion transporter that exchanges 3 Na^+ for each Ca^{2+} ion transported across the cell membrane. NCX is upregulated in CHF and may compensate for cytosolic Ca^{2+} removal impairments caused by reduced SERCA function.[16,17] Changes in NCX may affect repolarization, since the NCX may carry significant net inward current, particularly during later AP phases. By enhancing Ca^{2+} extrusion, NCX may conspire with reduced SR Ca^{2+} uptake to decrease SR Ca^{2+} stores and thereby to impair contractile function. Despite reduced Ca^{2+} stores, CHF-hearts are prone to arrhythmogenic delayed

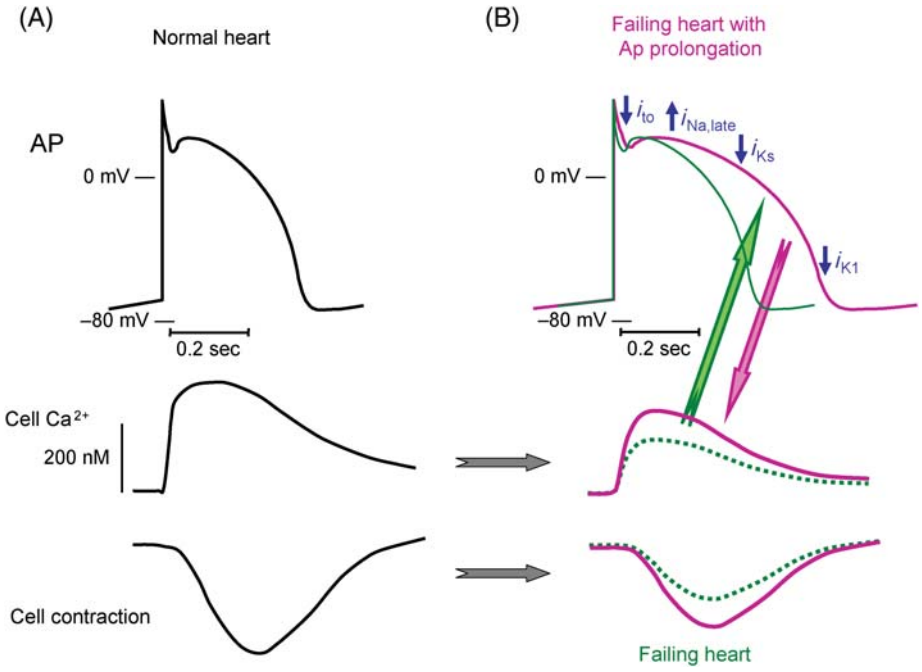

Figure 2 A schematic diagram showing the changes in Ca^{2+} handling and contractility and the potential compensatory function of ion-channel remodelling that causes action potential (AP) duration (APD) prolongation in congestive heart failure. (*A*) A normal cardiac AP, along with associated changes in free intracellular Ca^{2+} activity (upward deflection indicates increased Ca^{2+} concentration) and systolic cell contraction (downward deflection indicates cell length decrease). (*B*) Ca^{2+} concentrations and cell contraction in the failing heart are shown by the green dotted lines. Decreased systolic Ca^{2+} release impairs cellular contractility and causes APD-prolonging ion current remodelling (changes are indicated by the arrows indicating increases or decreases in specific currents). The results of APD-increasing ionic remodelling are indicated by the violet lines: longer APs improve cellular Ca^{2+} load, systolic Ca^{2+} release, and cellular contraction. However, this compensation comes at the expense of potential arrhythmogenic complications, as described in the text.

afterdepolarizations (DADs) and triggered arrhythmias due to abnormal SR function and diastolic Ca^{2+} release events. This complex subject is beyond the scope of the present paper: the interested reader is referred to a recent review article.[18]

Voltage-dependent K^+ currents are critical determinants of APD and their downregulation plays a major role in CHF-related APD prolongation. A reduction in I_{to}[12] and I_K, particularly the slowly activating component, I_{Ks}, are the most consistent findings.[7,14,19,20] Decreased maximum I_{to} conductance is most likely explained by reduced transcription and translation of Kv4.3 subunits, with a potential contribution from reduced expression of ancillary subunits such as KChIP2.[21–25] I_{Ks} downregulation has been observed in diseased human right ventricle,[19] and in animal models of tachypacing-induced CHF.[7,20,21,24] The reduction in I_{Ks} has been linked to reduced expression of the pore-forming subunit, KvLQT1, and of the accessory protein minK.[21] I_{Kr} remains largely unchanged during CHF.[7,19,21] I_{K1} is reduced in ventricular cardiomyocytes from terminally failing human hearts[19] and in several animal CHF models,[7,12,24,26] because of downregulation of the principal channel subunit Kir2.1.[24,25]

Because of limited space, the present paper focuses on ion current changes affecting repolarization. However, changes in cardiomyocyte coupling, mediated principally by connexins in gap junctions, can have major effects on the properties and spatial distribution of AP repolarization.[27] Important connexin remodelling occurs in a wide range of myocardial conditions.[18] The interested reader is referred to a recent detailed review of this complex subject.[28]

Although cardiomyocytes from CHF animals are generally hypertrophied, hypertrophy can occur without CHF. In bradycardia-associated hypertrophic remodelling, both I_{Kr} and I_{Ks} are reduced, producing a particularly arrhythmogenic environment.[20,21] In this paper, we have elected to deal with CHF and not with conditions causing cardiac hypertrophy without CHF. There are similarities and differences between these forms of remodelling.[21] The interested reader is referred to a pertinent review article.[13]

3.2 Activation of neurohumoral systems in congestive heart failure

Activation of the sympathetic nervous and the renin–angiotensin–aldosterone systems (RAAS) can significantly affect cardiac electrophysiology.[13] β-Adrenergic stimulation substantially increases I_{Ks} and I_{CaL}, but both increases and decreases in I_{Kr} have been observed.[29] Plasma catecholamine concentrations increase in CHF, reflecting increased sympathetic drive, and are significant mortality predictors.[30] Sustained β-adrenergic stimulation mimics many of the ion current changes occurring in CHF, including downregulation of I_{Ks} and I_{K1}.[31] The RAAS maintains haemodynamic stability via the regulation of vascular tone, salt and water homeostasis, and cardiac function. RAAS activity increases in CHF have detrimental effects on disease progression. Angiotensin-II and aldosterone regulate cardiac ion channels and promote structural remodelling.[32] They can prolong APD

by enhancing inward currents such as I_{Na}[33] and I_{CaL}[34,35] and reducing outward currents such as I_{to}[36,37] and I_{K1}.[38,39]

3.3 Arrhythmogenic mechanisms related to repolarization abnormalities in congestive heart failure

Repolarization reserve is substantially reduced during CHF, as evident from the downregulation of repolarizing currents, the upregulation of $I_{Na,late}$ and APD prolongation. Delayed ventricular repolarization can promote the generation of early afterdepolarizations (EADs), leading to triggered activity and ventricular tachyarrhythmias[6] including TdP.[40] Indeed, EADs have frequently been reported in failing ventricles.[7,19,41] A key event in EAD initiation is the time-dependent recovery of I_{CaL} from inactivation in a voltage range of steady-state current flow.[42] Reduced I_{K1} increases membrane resistance, allowing greater depolarization for a given inward current[26] and promoting the occurrence of DADs.[18,43] Alterations in I_{to}[44] and I_{Ks}[20,21] contribute towards repolarization abnormalities and cardiac arrhythmogenesis. Reductions in I_{Ks} can increase the APD-prolonging and TdP-inducing effects of I_{Kr} blockers, even without causing APD prolongation in the absence of I_{Kr} blockers.[21] Decreases in I_{K1} and I_{to} enhance the repolarization-delaying effects of I_{Kr} blockers in the specialized His–Purkinje system.[45] It is well known that sympathetic activation can trigger malignant arrhythmias,[46,47] and enhanced sympathetic tone, which augments I_{Ks} and I_{CaL},[48,49] can induce arrhythmogenic afterdepolarizations. Furthermore, the expression of I_{Ks} is heterogeneous across the heart and within the myocardial wall,[50,51] and reduction in I_{Ks} may lead to heterogeneous dispersion of refractoriness, providing a substrate for re-entrant arrhythmias. CHF-induced repolarization-reserve abnormalities may lead to exaggerated repolarization disturbances under circumstances that further affect repolarization, such as with repolarization-impairing channel-gene mutations,[52] or in response to factors such as hypokalemia, hypomagnesemia, repolarization-prolonging drugs or excess bradycardia.

4. Remodelling of repolarization during atrial fibrillation

Atrial fibrillation (AF) is the most common sustained arrhythmia in the developed world.[53] Although this arrhythmia occurs most frequently in the presence of cardiovascular diseases such as CHF, ischaemic, hypertensive, and valvular heart disease,[54] it can also occur in the absence of any discernable underlying cardiac pathology.[55] AF is often initially reversible, but becomes more persistent over time; brief episodes or paroxysmal AF may progress to sustained AF as a consequence of progressive electrophysiological remodelling.[56] Eventually, AF becomes resistant to sinus-rhythm conversion and maintenance, leading to 'permanent AF'.[57]

4.1 Atrial fibrillation-related electrical remodelling

During AF, APD tends to abbreviate,[58] likely as a compensatory mechanism to prevent the Ca^{2+} overload[59–61] that can result from rapid atrial rates.[62–64] The term 'electrical remodelling' with respect to AF was originally coined by Allessie and co-workers.[56] They demonstrated in a goat model that AF itself alters electrical properties to promote further AF. AF leads to abbreviated atrial refractoriness and increased vulnerability to AF induction, over both short-term (minutes) and longer-term (days) time courses.[56,58–60] Similar remodelling occurs in experimental animal models with sufficiently rapid atrial tachycardia.[65] Atrial remodelling may also include alterations in chamber size, cell ultrastructure, and fibrous tissue content, which constitute changes sometimes termed 'structural remodelling'.[56,66,67] The focus of this review is electrical remodelling, particularly as it affects APD: readers are directed to pertinent reviews for discussions of structural remodelling.[67–69]

4.2 Ionic basis for repolarization remodelling in atrial fibrillation

Attuel *et al.*,[70] provided early evidence of characteristic electrophysiological abnormalities in AF patients, including impaired refractoriness rate adaptation. This is a distinctive feature of AF-related remodelling,[56,58,61] and was subsequently shown to be caused by AF in man.[71] Early work in animal models,[61] subsequently confirmed in human studies,[57] indicated a prime role of I_{CaL} changes in AF-related APD alterations. More recent work also points to important alterations in K^+ currents.[18]

4.3 Changes in inward currents

In atrial cardiomyocytes from patients with chronic AF, no changes in Na^+ current-density or Na^+-channel α-subunit mRNA expression have been detected.[72] A positive shift in I_{Na}-inactivation voltage dependence has been observed, evidence of altered biophysical properties.[72] AF-induced changes in electrophysiology have been extensively studied in animal models of rapid atrial pacing,[65] where progressive decreases in I_{Na} and atrial conduction-slowing were detected.[73]

I_{CaL} is reduced by ~70% in human AF[72,74] and in atrial cells from a canine model,[61] contributing significantly to the loss of AP plateau. L-type Ca^{2+}-channel downregulation is a major contributor to APD and refractoriness decreases linked with AF,[61,64,72,74–76] whereas T-type Ca^{2+} channels do not appear to be affected.[61] Alterations in I_{CaL} may be explained by decreased α-subunit mRNA and protein expression.[77,78] Although these changes were not accompanied by altered voltage dependence, some studies suggest slowed I_{CaL} inactivation in AF.[74,78] These alterations may occur faster in animal models of AF compared with humans.[79,80]

Ca^{2+} overload inactivates I_{CaL} by binding to a high-affinity site on the channel and causing Ca^{2+}-dependent channel inactivation: this likely contributes importantly to short-term I_{CaL} decreases and APD/refractory period reductions.[58] In the longer term, persistent reductions in I_{CaL} are responsible for further changes in electrophysiological properties such as reduced APD and refractoriness.[56,73,81,82] Loss of I_{CaL} also contributes to diminished atrial contractility in AF that contributes to the thrombogenic risk.[83] There are several potential subcellular mechanisms by which Ca^{2+} overload and reduced I_{CaL} mediate structural, electrical, and contractile remodelling, including activation of cellular proteases such as calpains,[84,85] Ca^{2+}-dependent kinases or

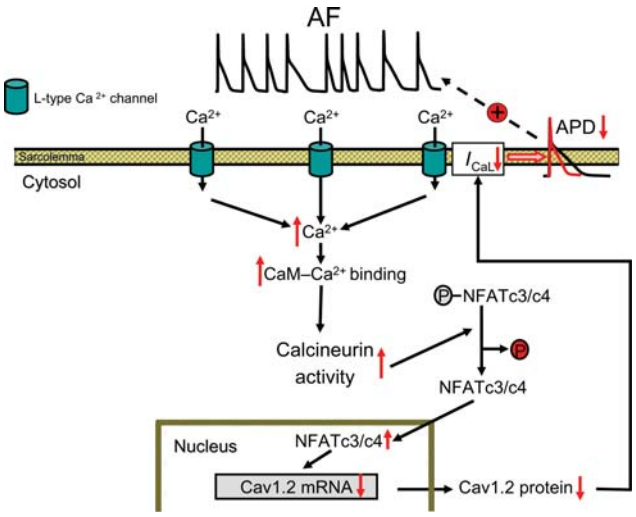

Figure 3 A schematic illustrating processes that contribute to reducing L-type Ca^{2+} current function in atrial fibrillation (AF). Changes resulting from AF are shown in red. Since Ca^{2+} enters the cell with each action potential (AP), an increased AP frequency will enhance cell Ca^{2+} loading. This induces enhanced Ca^{2+}–calmodulin binding, calcineurin activation, dephosphorylation and consequent nuclear transport of NFAT (nuclear factor of activated T-cells), followed by transcriptional downregulation of Ca^{2+} channels. Reduced inward Ca^{2+} current results in a shorter AP plateau and reduced APD (AP duration), which makes re-entrant AF more likely. CaM, calmodulin; Cav1.2, α-subunit of L-type Ca^{2+} channel.

phosphatases,[76,86] or inflammatory mechanisms associated with increased oxidative stress.[79]

Recent work has provided insights into the signalling mechanisms coupling increased cellular Ca^{2+} loading with I_{CaL} downregulation,[63,87,88] as illustrated in *Figure 3*. Increased heart rates during AF cause more Ca^{2+} to enter the cell. Intracellular Ca^{2+} concentration is increased, leading to Ca^{2+}–Calmodulin binding and enhanced calcineurin activity. Calcineurin, a Ca^{2+}-dependent phosphatase, dephosphorylates nuclear factor of activated T-cells, causing it to translocate to the nucleus and downregulate transcription of the gene encoding I_{CaL} α-subunits. I_{CaL} downregulation reduces the inward current flow during the AP, decreasing APD and promoting AF.

Cellular Ca^{2+} handling is also altered in AF, as evident from studies in atrial tissue-samples from atrial-tachypaced animals and AF patients.[89,90] Ca^{2+} transients are smaller and decay more slowly. Spontaneous release of Ca^{2+} from the SR, in the form of local and non-propagated sparks and more extensive Ca^{2+} release waves, have been observed in cells from AF patients, together with increased activity of the SR Ca^{2+} release channel;[91] however, no difference has been found in SR Ca^{2+} content between AF and non-AF patients.[91] Furthermore, a lack of change[80,90,92] and even reductions in the expression of Ca^{2+} handling proteins such as calsequestrin, phospholamban, SERCA or Ca^{2+} release channels have been reported in AF,[78,79,93,94] which would decrease releasable SR Ca^{2+}. One study shows increased protein expression of NCX in atria from patients with chronic AF,[90] conflicting with reports showing no change in NCX mRNA.[92] Discrepancies may relate to variations in patient populations, such as differences in types of underlying heart diseases, AF duration, the specific nature of drug therapy, etc. in various studies. The functional significance of these findings is still unclear, but altered Ca^{2+} handling and abnormal diastolic Ca^{2+} release events may initiate ectopic activity that acts on the remodelled re-entrant substrate to initiate AF.

4.4 Changes in outward currents

Alterations in the density and molecular composition of voltage-gated K^+ currents have been observed in cardiomyocytes from AF patients. I_{to} is reduced by ~60%,[64,72,92,95] which can be explained by downregulation of Kv4.3 mRNA[78,96,97] and protein expression,[78,97] resulting in a smaller number of membrane channels. In canine models, reductions in I_{to} occur within 24 h of atrial tachypacing.[61,75,98] I_{Kur}, predominantly found in human atria,[99] has been linked to Kv1.5-subunit expression.[100–102] The data regarding I_{Kur} in human AF subjects are inconsistent, with no change[64,72,96] or decreases in current,[95] Kv1.5 subunit mRNA[79] or protein expression reported.[78,95,97] I_{Kur} is unchanged in a canine model,[61] and the significance of reduced I_{Kur} in AF remains unclear. An important consideration is that the role of I_{Kur} in the AP depends heavily on AP morphology.[103] Although I_{Kur} inhibition delays early repolarization, this raises the AP plateau, tending to activate I_{Kr} and accelerate terminal repolarization, thus offsetting or even reversing APD prolongation.[103] The degree to which I_{Kr} enhancement occurs depends on AP morphology, with brief triangular APs such as those occurring with AF activating very little I_{Kr} and therefore allowing significant APD prolongation with I_{Kur} inhibition.[103,104] There are limited data available for delayed-rectifier K^+ currents, perhaps because of technical difficulty in preserving them in isolated cardiomyocytes. Functional data in human cardiomyocytes are lacking, but I_{Kr} and I_{Ks} remain unchanged in a canine AF model.[61] Decreased mRNA[78,79,105] and protein expression of HERG have been reported in AF patients,[97] but these could be related to underlying heart disease. Reported alterations in KvLQT1 and minK expression have been variable, with both increases[78,79] and decreases[78,79,105] having been described.

Alterations in inward-rectifier K^+ currents occur in AF and may play an important role in repolarization changes and arrhythmogenesis (*Figure 4*). I_{K1} is increased in AF patients[64,72,95,105,106] and in animal studies,[107] due to upregulation of Kir2.1 mRNA[105,106] and protein.[105] Increased I_{K1} hyperpolarizes the resting membrane under AF conditions.[106,108] Increased I_{K1} may result from mechanisms other than solely modified channel-subunit transcription and/or translation, since the single-channel open probability is slightly increased in chronic AF.[109] Possible explanations for these observations include altered dephosphorylation, which regulates I_{K1} single-channel function.[23,110]

Stimulation of muscarinic cholinergic receptors promotes AF.[111] Reduced agonist-induced I_{KACh} current-density and channel-subunit expression have been reported from cardiomyocytes of AF patients.[78,97,106] However, constitutively active I_{KACh}, which opens in the absence of cholinergic agonists, is upregulated by sustained atrial tachyarrhythmias in dogs[112] and humans.[109] AF-induced activation of constitutive I_{KACh} results in increased channel opening rates,[113] which may be due to altered channel phosphorylation.[114] *In vitro* studies suggest that constitutive I_{KACh} contributes significantly to repolarization remodelling caused by atrial

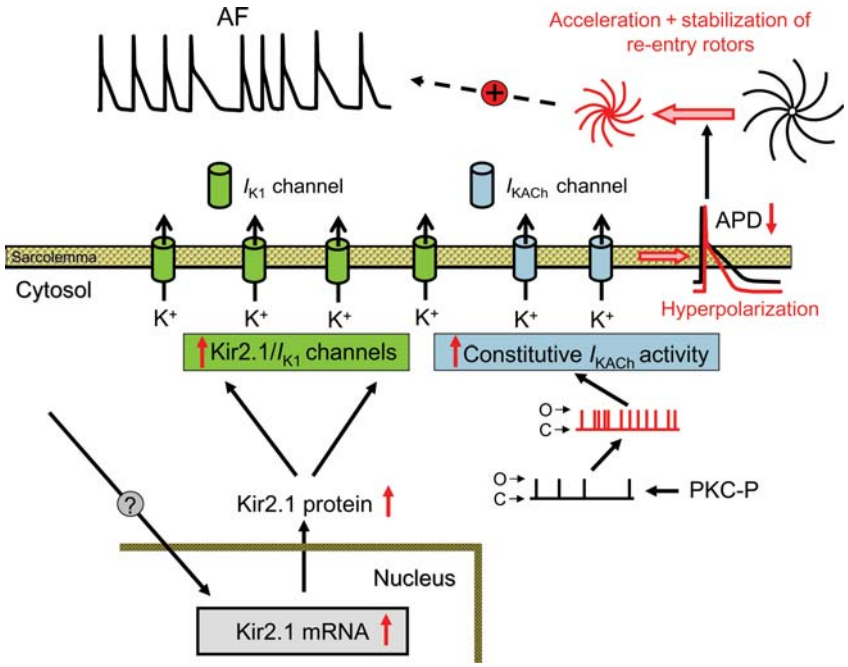

Figure 4 A schematic illustrating mechanisms and consequences of inward-rectifier K^+ current upregulation in atrial fibrillation (AF). Changes resulting from AF are shown in red. Increased production of I_{K1}-encoding Kir2.1 subunits through unknown signalling mechanisms enhances I_{K1}. Constitutive I_{KACh} function is amplified by an increased frequency of closed-to-open transitions in the absence of cholinergic agonists, possibly related to channel-phosphorylation changes, which increase channel open probability. Increases in both I_{K1} and constitutive I_{KACh} enhance inward-rectifier K^+ current in AF, resulting in hyperpolarization and abbreviation of the action potential (AP). Resting potential hyperpolarization removes I_{Na} inactivation and APD (AP duration) abbreviation shortens refractory period, causing acceleration and stabilization of AF-maintaining spiral-wave rotors that act as generators of fibrillatory activity. C and O, closed and open I_{KACh}-channel levels; PKC-P, regulation by PKC-induced channel phosphorylation.

tachyarrhythmias.[115] I_{KACh}-inhibition may thus be a promising AF-suppressing intervention.[115]

Relatively little information is available about the behaviour of ATP-regulated K^+ current (I_{KATP}), an important mediator of hypoxic/ischaemic APD abbreviation, in AF. The significance of changes in the expression of Kir6.2, the principle I_{KATP} α-subunit, remains to be elucidated as increases, decreases, and no change have been reported in AF.[78,97]

4.5 Arrhythmogenic mechanisms related to repolarization changes in atrial fibrillation

AF can be initiated by a variety of triggers, including premature atrial extrasystoles, bradycardia or rapidly firing ectopic foci located in the muscular sleeves of the pulmonary veins.[69] The principal factors determining whether AF will be initiated by atrial ectopic activity are atrial tissue properties that control the likelihood of re-entry. Atrial refractoriness influences the re-entrant wavelength, which determines the size of potential atrial re-entry circuits.[18] Decreased wavelength, as occurs with AF-related APD/refractory-period abbreviation, reduces the size and increases the number of atrial re-entrant circuits.[18,68,69] Reduced I_{Na} can slow conduction velocity and contribute to wavelength abbreviation.[73] Changes in repolarizing currents are spatially heterogeneous and lead to regionally variable changes in atrial refractoriness, which greatly increase the chance that atrial ectopic driver-foci can induce AF.[116,117] The importance of inward-rectifier current upregulation in AF-related arrhythmogenesis[115] may be related to the associated APD abbreviation and membrane hyperpolarization, which accelerate and stabilize re-entrant rotors that maintain the arrhythmia.[118]

5. Therapeutic implications of cardiac repolarization remodelling

Remodelling of cardiac repolarization has potentially important therapeutic implications. AP prolongation in CHF reduces repolarization reserve,[21,45] increasing the risk of TdP upon exposure to APD-prolonging agents, drugs that slow heart rate and K^+-losing diuretics. Reduced repolarization reserve may explain the increased risk of acquired long-QT syndrome with CHF[119] and may promote arrhythmia precipitation upon exposure to repolarization-impairing metabolic abnormalities.[120] Thus, great caution is needed with drugs that can impair repolarization when treating CHF patients. Prolonged APD enhances cellular Ca^{2+} entry, which helps to maintain contractility but may also interact with subcellular Ca^{2+} handling abnormalities to promote arrhythmogenesis. Caution is therefore needed in treating CHF patients with drugs that promote cellular Ca^{2+} entry, such as catecholamines and methylxanthines.

Atrial ERP abbreviation promotes AF induction and maintenance. AF-induced repolarization remodelling may explain the increased risk of AF recurrence over the first few days after electrical cardioversion.[121] Repolarization remodelling may also explain increased resistance of longer-lasting AF to I_{Kr}-inhibiting drugs,[122] since I_{Kr} contributes little to AP repolarization for the AF-remodelled AP-waveform.[103] Atrial remodelling may also present opportunities for drug development. The superiority of amiodarone in AF-prevention may relate

to its ability to suppress AF-related I_{CaL} downregulation and APD reduction[123] and anti-remodelling properties may identify potentially effective new anti-AF compounds such as statins.[124] Finally, AF-specific ionic mechanisms such as constitutive I_{KACh}-upregulation may provide leads for novel AF-suppressing targets.[125]

Conclusions

Compensatory changes in ion-transport mechanisms occur in response to a variety of cardiac disease processes. Adaptive responses attempt to maintain cardiac homeostasis, but these responses can generate arrhythmogenic substrates and triggers. An improved understanding of repolarization remodelling may allow for more specific and safer treatment approaches.

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