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 Ca²⁺, 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 Ca²⁺ (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_{Kr}) 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 Ca²⁺ 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_{Kr}, compared with fast-channel tissue.2 Nodal APs lack a plateau phase, have slow I_{CaL}-mediated phase 0 depolarization and show...
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. 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, or from increased expression of a $K^+$ current. 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. Prolongation of ventricular AP duration (APD), reflecting impaired repolarization, is a consistent finding in patients with CHF and in animal models. There is evidence that ventricular APD prolongation contributes to economic changes in CHF, reflecting impaired repolarization, and improves mechanical efficiency. It is therefore tempting to speculate that repolarization changes result from an attempt of the cell to maintain cell calcium and contractility as the CHF syndrome develops. 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, contributing to AP prolongation. $I_{CaL}$ remains largely unaltered in failing human hearts or experimental CHF-animal hearts, but reduced $I_{CaL}$ has also been reported in some studies. Cellular $Ca^{2+}$ handling is importantly altered in CHF. Sarcolemmal 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. 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. 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
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 \(I_{to}\) and \(I_{Ks}\), 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.\(^7,12,24,26\) 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.\(^13\) \(\beta\)-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 \(\beta\)-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.\(^{12}\) They can prolong APD

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**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.
by enhancing inward currents such as \( I_{Kr} \) and \( I_{CaL} \) and reducing outward currents such as \( I_{to} \) and \( I_{Kf} \).

### 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 \( h_{Na,late} \) and APD prolongation. Delayed ventricular repolarization can promote the generation of early afterdepolarizations (EADs), leading to triggered activity and ventricular tachyarrhythmias 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 \( I_{CaL} \) increases membrane resistance, allowing greater depolarization for a given inward current, and promoting the occurrence of DADs.\(^{18,43}\) Alterations in \( I_{to} \) and \( I_{Ks} \) 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 \( I_{Ks} \) and \( I_{CaL} \) 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 \( I_{CaL} \) 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 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 \( \alpha \)-subunit mRNA expression have been detected.\(^{72}\) A positive shift in \( h_{Na,late} \)-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 \( h_{Na} \) and atrial conduction-slowing were detected.\(^{73}\) \( I_{CaL} \) is reduced by ~70% in human AE\(^{72,74}\) 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 \( \alpha \)-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...
**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_{Kr} is reduced by ~60%,64,72,92,95 which can be explained by downregulation of Kv4.3 mRNA78,96,97 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.61,75,96 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 change64,72,99 or decreases in current,95 Kv1.5 subunit mRNA79 or protein expression reported.78,99,97 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_{K} and I_{Ks} remain unchanged in a canine AF model.61 Decreased mRNA78,79,105 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 increases78,79 and decreases78,79,105 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 patients54,72,95,105,106 and in animal studies,107 due to upregulation of Kir2.1 mRNA105,106 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.21,110

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 dogs112 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
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. 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. Decreased wavelength, as occurs with AF-related APD/refractory-period abbreviation, reduces the size and increases the number of atrial re-entrant circuits. Reduced 

which accelerate and stabilize re-entrant rotors that maintain the arrhythmia.

5. Therapeutic implications of cardiac repolarization remodelling

Remodelling of cardiac repolarization has potentially important therapeutic implications. AP prolongation in CHF reduces repolarization reserve, 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 and may promote arrhythmia precipitation upon exposure to repolarization-impairing metabolic abnormalities. Thus, great caution is needed with drugs that can impair repolarization when treating CHF patients. Prolonged APD enhances cellular Ca2+ entry, which helps to maintain contractility but may also interact with subcellular Ca2+ handling abnormalities to promote arrhythmogenesis. Caution is therefore needed in treating CHF patients with drugs that promote cellular Ca2+ 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. Repolarization remodelling may also explain increased resistance of longer-lasting AF to IKr-inhibiting drugs, since IKr contributes little to AP repolarization for the AF-remodeled AP-waveform. 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 \cite{12, 23} and anti-remodelling properties may identify potentially effective new anti-AF compounds such as statins. \cite{124} Finally, AF-specific ionic mechanisms such as constitutive $I_{KATP}$-upregulation may provide leads for novel AF-suppressing targets. \cite{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 responses attempt to maintain cardiac homeostasis, but in response to a variety of cardiac disease processes. Adaptive approaches.

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