Ion Channel Remodelling in Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia and is associated with substantial cardiovascular morbidity and mortality, with stroke being the most critical complication. Present drugs used for the therapy of AF (antiarrhythmics and anticoagulants) have major limitations, including incomplete efficacy, risks of life-threatening proarrhythmic events and bleeding complications. Non-pharmacological ablation procedures are efficient and apparently safe, but the very large size of the patient population allows ablation treatment of only a small number of patients. These limitations largely result from limited knowledge about the underlying mechanisms of AF and there is a hope that a better understanding of the molecular basis of AF may lead to the discovery of safer and more effective therapeutic targets. This article reviews the current knowledge about AF-related ion-channel remodelling and discusses how these alterations might affect the efficacy of antiarrhythmic drugs.

Keywords

Atrial fibrillation, remodelling, ion channels, mechanisms

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Atrial fibrillation (AF) is common and is associated with significant cardiovascular morbidity and mortality, with stroke being the most critical complication.[1,2] Drugs presently used for AF therapy have major limitations, including incomplete efficacy and risks of life-threatening proarrhythmic events (antiarrhythmic drugs) and bleeding complications (anticoagulants).[3] Non-pharmacological ablation procedures are efficient and apparently safe, but only a small number of patients can be treated.[4–6] These limitations largely result from the limited knowledge about the underlying mechanisms of AF. There is a hope that a better understanding of the molecular basis of AF may uncover safer and more effective therapeutic targets. In this article, current knowledge about AF-related ion-channel remodelling is reviewed and how such remodelling might affect the efficacy of antiarrhythmic drugs is discussed.

Fundamental Atrial Fibrillation Mechanisms

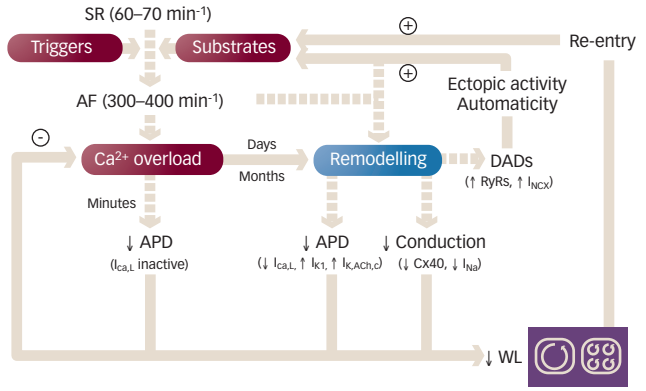
The mechanisms underlying AF induction and maintenance are incompletely understood, but it is generally accepted that re-entry is the major mechanism of AF maintenance. Re-entry induction requires an appropriate vulnerable substrate, as well as a trigger that initiates re-entry within the substrate (see *Figure 1*).

Single-circuit re-entry can maintain AF by functioning as a rapid driver that induces fibrillatory conduction. Multiple-circuit re-entry involves coexisting functional re-entry-circuits that maintain fibrillatory activity because the rate of new-circuit formation exceeds the rate of circuit extinction, continuously maintaining AF episodes. The likelihood of re-entry is determined by the tissue properties of conduction and refractoriness (for detailed discussion see[7,8]), with slow conduction and short refractoriness making persistence of re-entry more likely.

Another mechanism potentially involved in AF is ectopic activity, which is governed by factors controlling the occurrence of afterdepolarisations, primarily Ca^{2+}-handling abnormalities that can cause delayed afterdepolarisations (see *Figure 1*). Ectopic activity can also result from excessive action potential duration (APD) prolongation, which produces early afterdepolarisations. It remains to be shown whether early afterdepolarisations contribute to AF pathophysiology.

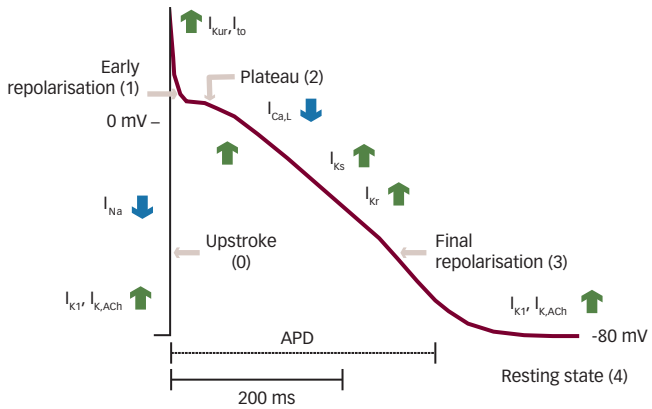
Prolonged episodes of AF alter atrial properties ('atrial remodelling') promoting AF maintenance (see *Figure 1*).[9] Changes in atrial structure or function that constitute atrial remodelling are key elements in the AF-substrate.[7,10] Remodelling increases the likelihood of ectopic firing or re-entry, thereby promoting AF initiation and/or maintenance. Ion-channel remodelling shortens the effective refractory period (ERP) by reducing APD.[7,10,11] Spatially heterogeneous ERP abbreviation promotes the conduction block and wave break underlying fibrillatory conduction and APD shortening contributes to AF-related atrial contractile dysfunction.[12–16] APD, and thus ERP, is determined by the balance between inward currents that depolarise and outward currents that repolarise cardiac myocytes (see *Figure 2*).

Figure 1: Mechanisms Underlying Promotion of Atrial Fibrillation by Atrial Ion Channel Remodelling



The rapid atrial rate increases potentially cytotoxic Ca^{2+} loading. Cells rapidly protect themselves by reducing L-type Ca^{2+} current ($I_{Ca,L}$) at the expense of decreased action potential duration (APD). Decreased APD abbreviates refractoriness and decreases the wavelength (WL) allowing for smaller re-entry circuits, a larger number of which can now be accommodated. In addition to decreased $I_{Ca,L}$, persistent AF increases the inward rectifier K^+ currents I_{K1} and constitutive $I_{K,ACh,c}$ and decreases connexin-40 (Cx40) and sodium current (I_{Na}) by changing either gene expression and/or protein regulation (proteolysis and altered phosphorylation or nitrosylation). This contributes to the APD shortening and conduction slowing that promote AF. AF is associated with abnormal function of ryanodine receptor channels (RyRs) producing increased diastolic sarcoplasmic reticulum Ca^{2+} leak. This is amplified by the generation of an enhanced inward Na^+-Ca^{2+}-exchange current (I_{NCX}), promoting delayed afterdepolarisations (DADs) and ectopic activity, further favouring AF maintenance. Ectopic activity from pulmonary veins may trigger AF. SR=sinus rhythm. See text for further details.

Figure 2: The Atrial Action Potential and Ion Currents



The action potential is controlled by ions flowing through ion channels (inward currents, blue arrow down; outward currents, green arrow up). The action potential upstroke (phase 0) results from a large sodium current (I_{Na}) with subsequent Ca^{2+} entry through L-type Ca^{2+} channels ($I_{Ca,L}$). During the plateau (phase 2) there is a balance between inward and outward currents. Repolarisation is governed by several K^+ currents including transient outward (I_{to}), ultra-rapid (I_{Kur}), rapid (I_{Kr}) and slow (I_{Ks}) delayed rectifier currents. I_{to} and I_{Kur} underlie early repolarisation (phase 1), I_{Kr} and I_{Ks} determine late repolarisation (phase 3), which brings the myocyte to the resting state (phase 4). The resting potential is determined by inward rectifier K^+ current (I_{K1}) and is modulated by acetylcholine-regulated K^+ current ($I_{K,ACh}$). APD=action potential duration. See text for further details.

Studies in animal models and in patients with chronic AF have shown that the following are major contributors to APD shortening:[17–24]

- decreased L-type Ca^{2+} current ($I_{Ca,L}$; reduced depolarisation power);
- increased inward rectifier K^+ current (I_{K1}; enhanced repolarisation power); and
- constitutively-active acetylcholine-independent K^+ current ($I_{K,ACh,c}$ enhanced repolarisation power).

Initially the resulting shortening of APD helps to compensate for initial Ca^{2+} overload (see *Figure 1*), but this occurs at the expense of decreased ERP, which favours re-entry.[7,25] The shorter refractoriness together with an unchanged sodium current (I_{Na}) may promote the induction of high-frequency sources (rotors). These undergo complex, spatially distributed conduction block patterns with wavefront fractionation manifesting as 'fibrillatory conduction' that maintains AF.[26]

Long-term AF causes profound alterations in atrial structure (cardiomyocyte hypertrophy, glycogen accumulation and interstitial fibrosis).[27,28] These lead to inhomogeneous conduction slowing that promotes the development of anatomically-fixed re-entry circuits. Atrial remodelling is clinically important as it explains the transition of paroxysmal to persistent AF,[9] the larger resistance of persistent AF to treatment[29,30] and higher AF recurrence rate in the first days after cardioversion.[31]

Ion-channel Remodelling in Atrial Fibrillation

As introduced above, the AF-related shortening of the APD can be attributed to decreased inward currents, enhanced outward K^+ currents or a combination of both. Depolarising inward I_{Na} and $I_{Ca,L}$ currents are balanced by a diversity of repolarising K^+ outward currents (see *Figure 2*). The main human atrial repolarising K^+ currents include:

- the transient outward current, I_{to};
- the ultra-rapidly activating delayed rectifier current, I_{Kur};
- the rapid (I_{Kr}) and the slow (I_{Ks}) activating delayed rectifier currents; and
- the three inward rectifier currents, I_{K1}, $I_{K,ACh}$ and ATP-sensitive $I_{K,ATP}$.

There is also evidence for the existence and role of Ca^{2+}-dependent small conductance potassium channels (SK channels) and transient receptor potential channels in shaping the human atrial AP (see below). Whether and how they contribute to remodelling in AF is currently unknown.

The molecular mechanisms leading to the repolarisation changes in AF are only partially understood. Increased atrial rate causes cellular Ca^{2+} loading,[32] which alters cellular Ca^{2+} signalling leading to functional $I_{Ca,L}$ inactivation, which attenuates initial Ca^{2+} overload.[33] Persistent AF produces sustained Ca^{2+} loading that is offset by the decreased function of $I_{Ca,L}$ and by increased Ca^{2+} extrusion via the Na^+-Ca^{2+}-exchanger. These compensatory changes limit cytotoxic Ca^{2+} influx but cause further ERP abbreviation, favouring multiple circuit re-entry (see *Figure 1*).[8,10,25] The increase in intracellular Ca^{2+} is likely a primary signal for altered gene expression[34] and regulation of ion channels.

Molecular Changes of I_{Na}

Sodium current (I_{Na}) density is reduced in a canine model of atrial tachycardia remodelling (ATR), with corresponding decreases in channel mRNA and protein expression.[17] Such changes could contribute to the atrial conduction slowing seen in AF. Despite this theory, Gaborit et al. did not find evidence of atrial I_{Na} changes at the genomic level in AF patients.[35] Data obtained in atrial myocytes from AF patients showed either unchanged[36] or only slightly reduced[37] I_{Na} amplitude.

Molecular Determinants of $I_{Ca,L}$ Alterations

Reduced $I_{Ca,L}$ density is a consistent finding in animal models of ATR and patients with AF.[17–19,38] In control cardiomyocytes, inhibition of $I_{Ca,L}$

with calcium-channel inhibitors mimics the APD abbreviation in ATR and AF.[17–19] Reduced $I_{Ca,L}$ was therefore initially considered as the only determinant of refractoriness shortening in ATR and AF. Subsequent studies, however, indicated important contributions of increased I_{K1} along with constitutively active $I_{K,ACh}$.[21–24,39–41] The molecular basis of decreased $I_{Ca,L}$ in ATR and AF is complex and likely depends partly on underlying heart disease.

Transcriptional down-regulation of the Cav1.2 subunit, due to initial Ca^{2+} overload, is one potential mechanism of reduced $I_{Ca,L}$ density.[34,42,43] Direct measurements demonstrated that rapid pacing quickly increases cardiomyocyte intracellular Ca^{2+}.[32]In addition to this, recent *in vitro* studies of tachypaced dog atrial cardiomyocytes directly confirmed that Ca^{2+} influx via $I_{Ca,L}$ itself and the related Ca^{2+} overload are major determinants of the transcriptional down-regulation of $I_{Ca,L}$. Here, Ca^{2+}-calmodulin/calcineurin-related mechanisms were implicated in modification of transcription.[34] Some subsequent studies at the mRNA and protein level confirmed the reductions in Cav1.2 subunit abundance,[35,44] whereas other reports found no change in protein amount or dihydropyridine receptor density in AF,[19,45,46] suggesting the existence of alternative mechanisms.

There is evidence for increased Ca^{2+}-channel dephosphorylation by increased activity of type-1 (PP1) and type-2A (PP2A) serine/threonine protein phosphatases in AF[19,46,47] that is expected to reduce the open probability, potentially explaining the decreased $I_{Ca,L}$ amplitude. Defective regulation of $I_{Ca,L}$ by inhibitory src-type tyrosine kinases may also participate in $I_{Ca,L}$ dysregulation.[46] S-nitrosylation of the Cav1.2 subunit is increased in AF and exogenously applied glutathione partially restores the AF-related $I_{Ca,L}$ reduction.[48] Thus, oxidative stress could play an important role in $I_{Ca,L}$ changes.

Finally, some, but not all, investigations detected decreased expression of accessory β_1, β_{2a}, β_{2b}, $\alpha_2\delta_2$ subunits.[19,35,38,45,49] These may also contribute to the reduction of $I_{Ca,L}$.

Mechanisms of Altered Voltage-gated K^+-currents

I_{to} amplitude is consistently reduced in animals with ATR and in AF patients.[10,17,38,43,50] The functional consequences of impaired I_{to} are unclear, but reduced I_{to} might facilitate wave propagation by indirectly increasing the upstroke velocity of the atrial AP.

In ATR and AF, reductions in I_{to} are paralleled by decreases in both mRNA and protein expression of the pore-forming Kv4.3 subunit,[43,50,51] with calpain-mediated proteolysis likely contributing to decreased Kv4.3 protein levels.[52,53] CaMKII activity is enhanced in ATR[15] and in AF patients.[54,55] CaMKII accelerates I_{to} inactivation, but the higher PP1 and PP2A activity in AF[19,46,47] could offset the enhanced CaMKII effect. Ca^{2+}-dependent protein phosphatases, such as calcineurin, may suppress Kv4.3 gene transcription via a nuclear factor of activated T-lymphocyte-dependent mechanism[56] because calcineurin activity is increased in AF.[57]

Results about the function of the ultra-rapid delayed-rectifier I_{Kur} are discrepant, showing either unchanged or reduced I_{Kur} function in AF.[50] The contribution of I_{Kur} to atrial repolarisation depends on AP morphology and is increased with short-duration triangular APs, as occur in AF. For this reason, I_{Kur} may contribute more strongly to atrial repolarisation in AF cardiomyocytes.[58,59]

Decreased[39,51,60] or unchanged[36,61,62] current amplitude and unaltered mRNA or reduced protein levels of the pore-forming Kv1.5 subunit are reported.[42,61,63,64] The inconsistent results regarding I_{Kur} function might result from variations in expression and posttranslational modifications of the principal channel α-subunit Kv1.5, including protein degradation due to increased proteolysis by calpains.[53] Intracellular redox state is shifted to increased oxidant production in ATR and AF[65,66] and Kv1.5 currents are inhibited by S-nitrosylation.[67] Variations in underlying cardiac diseases[35] and/or concomitant medication may contribute to some of the inconsistencies in various clinical studies.[50]

The delayed-rectifier currents I_{Kr} and I_{Ks} are not changed in experimental ATR[17] and information from AF patients is very limited, probably because of difficulties recording proper I_{kr} and I_{Ks} in human atrial myocytes isolated with the 'chunk' method. Initial molecular studies in AF patients have reported decreased mRNA and protein abundance of the HERG-subunit of I_{Kr} and varying expression changes in the α-subunit (KvLQT1) of I_{Ks}, along with increased mRNA and protein levels of the β-subunit minK.[35,50,63] One recent study detected higher I_{Ks} amplitude in left and right atrial myocytes of chronic AF patients and suggested enhanced I_{Ks} as an additional contributor to AF-related APD abbreviation.[68] The function of atrial I_{Kr} during AF is still unknown.

Molecular Basis of Altered Inward Rectifier K^+-current Function

The cardiomyocyte resting membrane potential is set primarily by background inward rectifier K^+ conductances. The resting membrane potential is more negative in AF,[21–24,41,69,70] which is consistent with the increased amplitude of inward rectifier K^+-current, I_{K1}, in both dogs with ATR and AF patients.[20–24,40,41,69,71]

Increased Kir2.1 mRNA[21,35,72] and protein levels[35,72] contribute to enhanced I_{K1} in clinical AF. In dogs with ATR of up to six weeks duration, however, Kir2.1 remains stable.[43] This suggests that increased Kir2.1 mRNA is likely to be a consequence of longstanding ATR or underlying clinical conditions in AF patients. Single-channel studies show that increased whole-cell I_{K1} may result from the enhanced open probability in AF.[22] The underlying molecular mechanisms remain to be determined. Despite this, channel phosphorylation reduces I_{K1} amplitude[73] and channel dephosphorylation due to increased phosphatase activity of PP1 and PP2A[19,46,47] could contribute to the increased I_{K1} activity in AF. MicroRNA-1 reciprocally regulates the Kir2.1 subunit expression of I_{K1} in coronary artery disease, contributing to arrhythmogenesis.[74] MicroRNA-1 levels are greatly reduced in human AF, possibly contributing to up-regulation of Kir2.1 subunits, leading to increased I_{K1}.[72]

Increased vagal activity strongly promotes AF by stabilising atrial re-entrant rotors and initiation of clinical AF is more likely under vagotonic conditions.[75] Acetylcholine released from vagal nerve endings stimulates cardiac muscarinic receptors (M-receptors) that activate $I_{K,ACh}$, which produces highly arrhythmogenic, spatially heterogeneous decreases in atrial ERP. In knock-out mice lacking $I_{K,ACh}$, M-receptor stimulation does not induce AF.[76] Besides activation by M-receptors, atrial $I_{K,ACh}$ is also stimulated by adenosine[77] and sphingosine-1 phosphate[78] receptors. The activation of $I_{K,ACh}$ in response to receptor stimulation is reduced, however, in ATR and AF patients.[20,21,69]

Recent work suggests that the reduced receptor-mediated $I_{K,ACh}$ activation is related to a loss of channel control by cardiac receptors. This leads to increased agonist-independent constitutive $I_{K,ACh}$, both in dogs with ATR[20,23,40] and in patients with chronic, but not paroxysmal, AF.[22,24,41] Blockade of constitutive $I_{K,ACh}$ suppresses APD abbreviation and AF promotion in ATR preparations,[23] indicating that constitutive $I_{K,ACh}$ contributes to ATR-induced atrial arrhythmogenesis.

Agonist-independent constitutive $I_{K,ACh}$ results from the enhanced open probability due to the increased frequency of channel openings.[22,40] mRNA and protein expression of Kir3.1 and Kir3.4 subunits are unchanged in experimental ATR.[40] In AF patients, however, the mRNA and protein levels of both subunits are decreased.[21,35,41,42,63]

In atrial myocardium, $I_{K,ACh}$ is localised in a macromolecular complex including catalytic subunits of PKA, PKC, CaMKII, PP1 and PP2A.[79] Altered composition of this complex in AF may lead to abnormal phosphorylation-dependent $I_{K,ACh}$ regulation. Blockade of PKC reduces, whereas inhibition of protein phosphatases increases, constitutive $I_{K,ACh}$ activity[80] and the abundance of PKCε protein is enhanced in AF.[24] This clearly suggests that PKC-hyperphosphorylation of $I_{K,ACh}$ may underlie the AF-related development of agonist-independent constitutive $I_{K,ACh}$ activity.[81]

ATP-sensitive inward rectifier K^+ currents ($I_{K,ATP}$) are important contributors to ischemia-induced changes in cardiac electrophysiology and atrial ischaemia is likely to occur, particularly in persistent AF. $I_{K,ATP}$ amplitude is higher in myocytes from AF patients under ischaemic conditions,[82] whereas $I_{K,ATP}$ activation in response to agonists like rilmakalim is strongly limited.[83]

Data about expression of the pore-forming Kir6.2 subunit are inconsistent.[42,63] They suggest a complex and perhaps clinical condition-dependent regulation of $I_{K,ATP}$ in AF.

Remodelling of Ion Channels Involved in Atrial Conduction

Ventricular expression and function of the major cardiac connexin, connexin-43, is reduced by structural remodelling (gap junctional remodelling) and these changes correlate with pro-arrhythmic conduction slowing.[84] Phosphorylation of connexins by different kinases determines connexin trafficking, gap junction assembly and channel-gating properties. Dephosphorylation and redistribution to lateral cell borders are prominent and important determinants of cardiac conduction disturbances.[84,85]

Relatively little is known about gap junctional remodelling in the atria, with discrepant results in the literature showing unchanged, increased and decreased connexin isoform expression.[10,35,86] It is possible that the specific connexin alteration depends on the time course, underlying cardiac pathology and animal model used.[87,88] Spatially heterogeneous connexin-40 remodelling is observed in the well-controlled goat AF-remodelling system.[89] This is consistent with the extensive clinical evidence pointing to disturbances in connexin-40 as a basis for genetic AF predisposition.[90–92]

Remodelling of Other Plasmalemmal Ion Channels

Canonical transient receptor potential channels contribute to abnormal Ca^{2+} signalling in hypertrophy (for recent review see[93]) and are potentially involved in arrhythmias.[94] Type-1 and type-3 transient receptor-potential channels are expressed in the human atrium of patients with diseased hearts. Transient receptor potential channel 3 protein expression is higher in animals with sustained AF and in AF patients.[95] This suggests transient receptor potential channel 3 proteins as potential novel contributors to AF-related ion-channel remodelling.

In a recent genome-wide association study, a single nucleotide polymorphism that lies within the gene encoding a specific small conductance K^+ channel (SK3) was associated with lone AF.[96] Human atria express three different SK channel subunits (SK1–3).[97] Overexpression of SK2 channels in mice shortens atrial AP,[98] whereas SK2 knock-out prolongs APD and induces early afterdepolarisations.[99] SK channels appear to contribute to pacing-induced shortening of APD in rabbit pulmonary veins.[98] Although SK2 and SK3 channels are potential novel contributors to AF-related ion-channel remodelling, their precise roles in atrial remodelling require further extensive examination and validation.

Remodelling of Ion Channels and Transporters that Contribute to Atrial Ectopic Activity

Multiple studies have shown that abnormal SR Ca^{2+} handling may play a central role in the initiation and/or maintenance of AF in humans.[100–107] Defective Ca^{2+} handling was shown to predispose to spontaneous sarcoplasmic reticulum (SR) Ca^{2+} release events in atrial myocytes from patients with chronic AF.[100–103] SR Ca^{2+} load is not increased in chronic AF patients,[100,103,105] suggesting that these spontaneous SR Ca^{2+} releases most likely occurred because of alterations in ryanodine receptor channels (RyR2) and the resulting increase in diastolic SR Ca^{2+} leak. Phosphorylation of RyR2 at Ser2808 (or Ser2809, depending on the species)[101] by PKA and at Ser2814 (or Ser2815 depending on species)[54,103,108] by CaMKII is higher in dogs with pacing-induced chronic AF and patients with chronic AF. These posttranslational alterations increase the sensitivity of RyR2 to cytosolic Ca^{2+} and enhance the open probability,[101] providing a possible molecular mechanism for aberrant RyR2 function in AF.

It is very likely that enhanced RyR2 activity plays a role in AF pathogenesis, as mice with a gain-of-function mutation in RyR2 or knock-out of the RyR2-inhibitory FKBP12.6 subunit exhibit an increased susceptibility to pacing-induced AF.[54,109] Using these mice models it was demonstrated that increased SR Ca^{2+} leak in atrial myocytes can promote triggered activity and atrial arrhythmias.

Altered RyR2 function in chronic AF is accompanied by an increase in Na^+-Ca^{2+}-exchanger expression and function.[12,47,103,105,110] This suggests that diastolic SR Ca^{2+} leak can be amplified by the Na^+-Ca^{2+}-exchanger, thereby triggering delayed afterdepolarisations and subsequent ectopic focal discharges or facilitating micro-re-entry circuits promoting AF maintenance. In addition to this, IP_3 receptor (IP_3R2)-mediated SR Ca^{2+} release may also facilitate SR Ca^{2+} leak via RyRs, which promotes atrial arrhythmogenesis,[111] and protein expression of IP_3R2 is increased in a model of ATR.[112] IP_3R2-coupled amplification of atrial SR Ca^{2+} release events and related arrhythmogenesis may thus be an important contributor to AF-related ectopic activity.

Therapeutic Consequences of Ion-channel Remodelling

The changes in ion-channel function caused by AF alter the response to antiarrhythmic drugs, principally making AF more drug-resistant.[113]

A poorer response of more prolonged AF has been shown for both Na^+- and K^+-channel blockers.[29,30,58]

Early detection and termination of AF increases the clinical effectiveness of pharmacological cardioversion.[30] A strategy of early cardioversion:

- reduces atrial remodelling;[114]
- prevents atrial dysfunction;[115]
- reduces atrial size; and[116]
- may prolong sinus-rhythm maintenance in the post-cardioversion period.[116,117]

Despite this, there is little evidence from clinical trials for the therapeutic value of an early cardioversion strategy.[114]

Ion-channel remodelling provides a potential antiarrhythmic drug target. Both the T-type Ca^+-channel blocker mibefradil[118] and amiodarone[119] suppress APD abbreviation as an index of ion-channel remodelling. $I_{Ca,L}$[118,120] K^+-channel and Na^+-channel blockers, however, are mostly ineffective.[119] It has been assumed that prevention of ion-channel remodelling (suppression of $I_{Ca,L}$ reduction) may contribute to amiodarone's superior efficacy in AF.[119] Bepridil, a L- and T-type Ca^{2+}-channel blocker, also suppresses ion-channel remodelling indices, an action that may explain bepridil's unusual ability to convert long-standing AF.[121]

Drugs targeting atrial-selective channels such as I_{Kur} and constitutive $I_{K,ACh}$ provide a promising approach because they do not affect ventricular repolarisation.[33] However, due to the remodelling effectiveness of I_{Kur} blockers (e.g. AVE0118) is reduced in patients with chronic AF.[59]

Increased inward rectifier K^+ currents, such as constitutive $I_{K,ACh}$, are more effective at stabilising and accelerating AF-sustaining rotors than reduction of $I_{Ca,L}$.[122] Selective inhibition of $I_{K,ACh}$ with the $I_{K,ACh}$-blocker tertiapin prolongs APD in ATR-remodelled canine preparations and suppresses tachyarrhythmias.[23] AVE0118 and flecainide both inhibit constitutive $I_{K,ACh}$ in chronic AF patients,[41] an effect that might contribute to their effectiveness in terminating AF. However, although $I_{K,ACh}$ pore-channel blockers effectively terminate AF, they could also have off-target effects in the brain, gastrointestinal and urinary tracts. Despite this, targeting the pathology-specific molecular mechanisms of constitutive $I_{K,ACh}$ may be an effective and safe anti-AF approach that does not interfere with physiological cholinergic agonist-stimulated $I_{K,ACh}$ function.

There is emerging evidence of increased diastolic SR Ca^{2+} leak through RyR2 channels and enhanced Na^+-Ca^{2+}-exchanger function. This may cause delayed after depolarisations and triggered activity contributing to AF maintenance. Such effects suggest that the development of new drugs specifically targeting arrhythmogenic diastolic SR Ca^{2+} leak might offer unique therapeutic opportunities to reduce atrial arrhythmogenesis by normalising SR Ca^{2+} handling (for detailed discussions see[33,106,123]).

Inflammation and tissue oxidation are believed to be important mediators in atrial remodelling.[124] Drugs with anti-inflammatory and antioxidant properties, such as glucocorticoids[125] and statins,[126] suppress atrial electrical remodelling, and have shown some clinical value in preventing AF recurrence.[127,128] Suppression of ion-channel remodelling may thus prove to be a useful principle, as either a primary or adjunct property of new antiarrhythmic drugs.

Conclusions

The past decade has provided important insights into key determinants of ion-channel remodelling in both experimental paradigms and clinical AF. Despite major advances, understanding about the underlying molecular mechanisms leading to and perpetuating ion-channel remodelling during AF is very limited. Better knowledge and deeper insights into the molecular mechanisms underlying AF may help to identify new and atrial-selective drug targets for the improved treatment of AF. ■

1. Pedersen OD, Abildstrom SZ, Ottesen MM, et al., Increased risk of sudden and non-sudden cardiovascular death in patients with atrial fibrillation/flutter following acute myocardial infarction, *Eur Heart J*, 2006;27:290–5.
2. Tsang TS, Miyasaka Y, Barnes ME, et al., Epidemiological profile of atrial fibrillation: a contemporary perspective, *Prog Cardiovasc Dis*, 2005;48:1–8.
3. Dobrev D, Nattel S, New antiarrhythmic drugs for treatment of atrial fibrillation, *Lancet*, 2010;375:1212–23.
4. Riley MJ, Marrouche NF, Ablation of atrial fibrillation, *Curr Probl Cardiol*, 2006;31:361–90.
5. Nattel S, Carlsson L, Innovative approaches to anti-arrhythmic drug therapy, *Nat Rev Drug Discov*, 2006;5:1034–49.
6. Nattel S, Opie LH, Controversies in atrial fibrillation, *Lancet*, 2006;367:262–72.
7. Nattel S, Burstein B, Dobrev D, Atrial remodelling and atrial fibrillation: mechanisms and implications, *Circ Arrhythm Electrophysiol*, 2008;1:62–73.
8. Nattel S, New ideas about atrial fibrillation 50 years on, *Nature*, 2002;415:219–26.
9. Wijffels MC, Kirchhof CJ, Dorland R, et al., Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats, *Circulation*, 1995;92:1954–68.
10. Nattel S, Maguy A, Le Bouter S, et al., Arrhythmogenic ion-channel remodeling in the heart: heart failure, myocardial infarction, and atrial fibrillation, Physiol Rev, 2007;87:425–56.
11. Dobrev D, Electrical remodeling in atrial fibrillation, *Herz*, 2006;31:108–12; quiz 142–3.
12. Schotten U, Greiser M, Benke D, et al., Atrial fibrillation-induced atrial contractile dysfunction: a tachycardiomyopathy of a different sort, *Cardiovasc Res*, 2002;53:192–201.
13. Sun H, Gaspo R, Leblanc N, et al., Cellular mechanisms of atrial contractile dysfunction caused by sustained atrial tachycardia, *Circulation*, 1998;98:719–27.
14. Yeh YH, Wakili R, Qi XY, et al., Calcium-handling abnormalities underlying atrial arrhythmogenesis and contractile dysfunction in dogs with congestive heart failure, *Circ Arrhythm Electrophysiol*, 2008;1(2):93–102.
15. Wakili R, Yeh YH, Qi XY, et al., Multiple potential molecular contributors to atrial hypocontractility caused by atrial tachycardia remodeling in dogs, *Circ Arrhythm Electrophysiol*, 2010;3(5):530–41.
16. Greiser M, Neuberger HR, Harks E, et al., Distinct contractile and molecular differences between two goat models of atrial dysfunction: AV block-induced atrial dilatation and atrial fibrillation, *J Mol Cell Cardiol*, 2009;46:385–94.
17. Yue L, Feng J, Gaspo R, et al., Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation, *Circ Res*, 1997;81:512–25.
18. Van Wagoner DR, Pond AL, Lamorgese M, et al., Atrial L-type Ca2+ currents and human atrial fibrillation, *Circ Res*, 1999;85:428–36.
19. Christ T, Boknik P, Wohrl S, et al., L-type Ca2+ current downregulation in chronic human atrial fibrillation is associated with increased activity of protein phosphatases, *Circulation*, 2004;110:2651–7.
20. Ehrlich JR, Cha TJ, Zhang L, et al., Characterization of a hyperpolarization-activated time-dependent potassium current in canine cardiomyocytes from pulmonary vein myocardial sleeves and left atrium, *J Physiol*, 2004;557:583–97.
21. Dobrev D, Graf E, Wettwer E, et al., Molecular basis of downregulation of G-protein-coupled inward rectifying K(+) current (I(K,ACh) in chronic human atrial fibrillation: decrease in GIRK4 mRNA correlates with reduced I(K,ACh) and muscarinic receptor-mediated shortening of action potentials, *Circulation*, 2001;104:2551–7.
22. Dobrev D, Friedrich A, Voigt N, et al., The G protein-gated potassium current I(K,ACh) is constitutively active in patients with chronic atrial fibrillation, *Circulation*, 2005;112:3697–706.
23. Cha TJ, Ehrlich JR, Chartier D, et al., Kir3-based inward rectifier potassium current: potential role in atrial tachycardia remodeling effects on atrial repolarization and arrhythmias, *Circulation*, 2006;113:1730–7.
24. Voigt N, Friedrich A, Bock M, et al., Differential phosphorylation-dependent regulation of constitutively active and muscarinic receptor-activated IK,ACh channels in patients with chronic atrial fibrillation, *Cardiovasc Res*, 2007;74:426–37.
25. Dobrev D, Nattel S, Calcium handling abnormalities in atrial fibrillation as a target for innovative therapeutics, *J Cardiovasc Pharmacol*, 2008;52:293–9.
26. Berenfeld O, Zaitsev AV, Mironov SF, et al., Frequency-dependent breakdown of wave propagation into fibrillatory conduction across the pectinate muscle network in the isolated sheep right atrium, *Circ Res*, 2002;90:1173–80.
27. Allessie M, Ausma J, Schotten U, Electrical, contractile and structural remodeling during atrial fibrillation, *Cardiovasc Res*, 2002;54:230–46.
28. Burstein B, Nattel S, Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation, *J Am Coll Cardiol*, 2008;51:802–9.
29. Duytschaever M, Blaauw Y, Allessie M, Consequences of atrial electrical remodeling for the anti-arrhythmic action of class IC and class III drugs, *Cardiovasc Res*, 2005;67:69–76.
30. Tieleman RG, Van Gelder IC, Bosker HA, et al., Does flecainide regain its antiarrhythmic activity after electrical cardioversion of persistent atrial fibrillation?, *Heart Rhythm*, 2005;2:223–30.
31. Okumura Y, Watanabe I, Nakai T, et al., Recurrence of atrial fibrillation after internal cardioversion of persistent atrial fibrillation: prognostic importance of electrophysiologic parameters, *Circ J*, 2005;69:1514–20.
32. Sun H, Chartier D, Leblanc N, et al., Intracellular calcium changes and tachycardia-induced contractile dysfunction in canine atrial myocytes, *Cardiovasc Res*, 2001;49:751–61.
33. Dobrev D, New concepts in understanding and modulating atrial repolarisation in patients with atrial fibrillation, *J Interv Card Electrophysiol*, 2008;22:107–10.
34. Qi XY, Yeh YH, Xiao L, et al., Cellular signaling underlying

atrial tachycardia remodeling of L-type calcium current, *Circ Res*, 2008;103:845–54.
35. Gaborit N, Steenman M, Lamirault G, et al., Human atrial ion channel and transporter subunit gene-expression remodeling associated with valvular heart disease and atrial fibrillation, *Circulation*, 2005;112:471–81.
36. Bosch RF, Zeng X, Grammer JB, et al., Ionic mechanisms of electrical remodeling in human atrial fibrillation, *Cardiovasc Res*, 1999;44:121–31.
37. Sossalla S, Kallmeyer B, Wagner S, et al., Altered Na(+) currents in atrial fibrillation effects of ranolazine on arrhythmias and contractility in human atrial myocardium, *J Am Coll Cardiol*, 2010;55:2330–42.
38. Bosch RF, Scherer CR, Rub N, et al., Molecular mechanisms of early electrical remodeling: transcriptional downregulation of ion channel subunits reduces I(Ca,L) and I(to) in rapid atrial pacing in rabbits, *J Am Coll Cardiol*, 2003;41:858–69.
39. Van Wagoner DR, Pond AL, McCarthy PM, et al., Outward K+ current densities and Kv1.5 expression are reduced in chronic human atrial fibrillation, *Circ Res*, 1997;80:772–81.
40. Voigt N, Maguy A, Yeh YH, et al., Changes in I K, ACh single-channel activity with atrial tachycardia remodelling in canine atrial cardiomyocytes, *Cardiovasc Res*, 2008;77:35–43.
41. Voigt N, Trausch A, Knaut M, et al., Left-to-right atrial inward-rectifier potassium current gradients in patients with paroxysmal versus chronic atrial fibrillation, *Circ Arrhythm Electrophysiol*, 2010;3(5):472–80.
42. Brundel BJ, Van Gelder IC, Henning RH, et al., Ion channel remodeling is related to intraoperative atrial effective refractory periods in patients with paroxysmal and persistent atrial fibrillation, *Circulation*, 2001;103:684–90.
43. Yue L, Melnyk P, Gaspo R, et al., Molecular mechanisms underlying ionic remodeling in a dog model of atrial fibrillation, *Circ Res*, 1999;84:776–84.
44. Klein G, Schröder F, Vogler D, et al., Increased open probability of single cardiac L-type calcium channels in patients with chronic atrial fibrillation. Role of phosphatase 2A, *Cardiovasc Res*, 2003;59:37–45.
45. Schotten U, Haase H, Frechen D, et al., The L-type Ca2+-channel subunits alpha1C and beta2 are not downregulated in atrial myocardium of patients with chronic atrial fibrillation, *J Mol Cell Cardiol*, 2003;35:437–43.
46. Greiser M, Halaszovich CR, Frechen D, et al., Pharmacological evidence for altered src kinase regulation of I (Ca,L) in patients with chronic atrial fibrillation, *Naunyn Schmiedebergs Arch Pharmacol*, 2007;375:383–92.
47. El-Armouche A, Boknik P, Eschenhagen T, et al., Molecular determinants of altered Ca2+ handling in human chronic atrial fibrillation, *Circulation*, 2006;114:670–80.
48. Carnes CA, Janssen PM, Ruehr ML, et al., Atrial glutathione content, calcium current, and contractility, *J Biol Chem*, 2007;282:28063–73.
49. Grammer JB, Zeng X, Bosch RF, et al., Atrial L-type Ca2+-channel, beta-adrenorecptor, and 5-hydroxytryptamine type 4 receptor mRNAs in human atrial fibrillation, *Basic Res Cardiol*, 2001;96:82–90.
50. Dobrev D, Ravens U, Remodeling of cardiomyocyte ion channels in human atrial fibrillation, *Basic Res Cardiol*, 2003;98:137–48.
51. Christ T, Wettwer E, Voigt N, et al., Pathology-specific effects of the IKur/Ito/IK,ACh blocker AVE0118 on ion channels in human chronic atrial fibrillation, *Br J Pharmacol*, 2008;154:1619–30.
52. Brundel BJ, Ausma J, van Gelder IC, et al., Activation of proteolysis by calpains and structural changes in human paroxysmal and persistent atrial fibrillation, *Cardiovasc Res*, 2002;54:380–89.
53. Goette A, Arndt M, Rocken C, et al., Calpains and cytokines in fibrillating human atria, *Am J Physiol Heart Circ Physiol*, 2002;283:H264–72.
54. Chelu MG, Sarma S, Sood S, et al., Calmodulin kinase II-mediated sarcoplasmic reticulum Ca2+ leak promotes atrial fibrillation in mice, *J Clin Invest*, 2009;119:1940–51.
55. Tessier S, Karczewski P, Krause EG, et al., Regulation of the transient outward K(+) current by Ca(2+)/calmodulin-dependent protein kinases II in human atrial myocytes, *Circ Res*, 1999;85:810–9.
56. Rossow CF, Dilly KW, Santana LF, Differential calcineurin/NFATc3 activity contributes to the Ito transmural gradient in the mouse heart, *Circ Res*, 2006;98:1306–13.
57. Bukowska A, Lendeckel U, Hirte D, et al., Activation of the calcineurin signaling pathway induces atrial hypertrophy during atrial fibrillation, *Cell Mol Life Sci*, 2006;63:333–42.
58. Courtemanche M, Ramirez RJ, Nattel S, Ionic targets for drug therapy and atrial fibrillation-induced electrical remodeling: insights from a mathematical model, *Cardiovasc Res*, 1999;42:477–89.
59. Wettwer E, Hála O, Christ T, et al., Role of IKur in controlling action potential shape and contractility in the human atrium: influence of chronic atrial fibrillation, *Circulation*, 2004;110:2299–306.
60. Brandt MC, Priebe L, Bohle T, et al., The ultrarapid and the transient outward K(+) current in human atrial fibrillation. Their possible role in postoperative atrial fibrillation, *J Mol Cell Cardiol*, 2000;32:1885–96.
61. Grammer JB, Bosch RF, Kuhlkamp V, et al., Molecular remodeling of Kv4.3 potassium channels in human atrial fibrillation, *J Cardiovasc Electrophysiol*, 2000;11:626–33.
62. Workman AJ, Kane KA, Rankin AC, The contribution of ionic currents to changes in refractoriness of human atrial myocytes associated with chronic atrial fibrillation, *Cardiovasc Res*, 2001;52:226–35.
63. Brundel BJ, Van Gelder IC, Henning RH, et al., Alterations in potassium channel gene expression in atria of patients with persistent and paroxysmal atrial fibrillation: differential regulation of protein and mRNA levels for K+ channels, *J Am Coll Cardiol*, 2001;37:926–32.
64. Ellinghaus P, Scheubel RJ, Dobrev D, et al., Comparing the global mRNA expression profile of human atrial and ventricular myocardium with high-density oligonucleotide arrays, *J Thorac Cardiovasc Surg*, 2005;129:1383–90.
65. Dudley SC, Jr., Hoch NE, McCann LA, et al., Atrial fibrillation increases production of superoxide by the left atrium and left atrial appendage: role of the NADPH and xanthine oxidases, *Circulation*, 2005;112:1266–73.
66. Kim YM, Guzik TJ, Zhang YH, et al., A myocardial Nox2 containing NAD(P)H oxidase contributes to oxidative stress in human atrial fibrillation, *Circ Res*, 2005;97:629–36.
67. Núñez L, Vaquero M, Gomez R, et al., Nitric oxide blocks hKv1.5 channels by S-nitrosylation and by a cyclic GMP-dependent mechanism, *Cardiovasc Res*, 2006;72:80–9.
68. Caballero R, de la Fuente MG, Gómez R, et al., In humans, chronic atrial fibrillation decreases the transient outward current and ultrarapid component of the delayed rectifier current differentially on each atria and increases the slow component of the delayed rectifier current in both, *J Am Coll Cardiol*, 2010;55:2346–54.
69. Dobrev D, Wettwer E, Kortner A, et al., Human inward rectifier potassium channels in chronic and postoperative atrial fibrillation, *Cardiovasc Res*, 2002;54:397–404.
70. Cha TJ, Ehrlich JR, Zhang L, et al., Atrial tachycardia remodeling of pulmonary vein cardiomyocytes: comparison with left atrium and potential relation to arrhythmogenesis, *Circulation*, 2005;111:728–35.
71. Cha TJ, Ehrlich JR, Zhang L, et al., Atrial ionic remodeling induced by atrial tachycardia in the presence of congestive heart failure, *Circulation*, 2004;110:1520–6.
72. Girmatsion Z, Biliczki P, Bonauer A, et al., Changes in microRNA-1 expression and IK1 up-regulation in human atrial fibrillation, *Heart Rhythm*, 2009;6:1802–9.
73. Karle CA, Zitron E, Zhang W, et al., Human cardiac inwardly-rectifying K+ channel Kir(2.1b) is inhibited by direct protein kinase C-dependent regulation in human isolated cardiomyocytes and in an expression system, *Circulation*, 2002;106:1493–9.
74. Yang B, Lin H, Xiao J, et al., The muscle-specific microRNA miR-1 regulates cardiac arrhythmogenic potential by targeting GJA1 and KCNJ2, *Nat Med*, 2007;13:486–91.
75. Kneller J, Zou R, Vigmond EJ, et al., Cholinergic atrial fibrillation in a computer model of a two-dimensional sheet of canine atrial cells with realistic ionic properties, *Circ Res*, 2002;90:E73–87.
76. Kovoor P, Wickman K, Maguire CT, et al., Evaluation of the role of I(KACh) in atrial fibrillation using a mouse knockout model, *J Am Coll Cardiol*, 2001;37:2136–43.
77. Dobrev D, Wettwer E, Himmel HM, et al., G-Protein beta(3)-subunit 825T allele is associated with enhanced human atrial inward rectifier potassium currents, *Circulation*, 2000;102:692–7.
78. Himmel HM, Meyer Zu Heringdorf D, et al., Evidence for Edg-3 receptor-mediated activation of I(K.ACh) by sphingosine-1-phosphate in human atrial cardiomyocytes, *Mol Pharmacol*, 2000;58:449–54.
79. Nikolov EN, Ivanova-Nikolova TT, Coordination of membrane excitability through a GIRK1 signaling complex in the atria, *J Biol Chem*, 2004;279:23630–6.
80. Voigt N, Makary S, Nattel S, et al., Voltage-clamp-based methods for the detection of constitutively active acetylcholine-gated IK,ACh channels in the diseased heart, *Methods Enzymol*, 2010;484:653–75.
81. Makary S, Maguy A, Wakili R, et al., Mechanisms underlying activation of constitutive acetylcholine-regulated potassium channels by atrial tachycardia remodeling, *Circulation*, 2009;120:S664.
82. Wu G, Huang CX, Tang YH, et al., ATP current density and allosteric modulation during chronic atrial fibrillation, *Chin Med J (Engl)*, 2005;118:1161–6.
83. Balana B, Dobrev D, Wettwer E, et al., Decreased ATP-sensitive K(+) current density during chronic human atrial fibrillation, *J Mol Cell Cardiol*, 2003;35:1399–405.
84. Akar FG, Spragg DD, Tunin RS, et al., Mechanisms underlying conduction slowing and arrhythmogenesis in nonischemic dilated cardiomyopathy, *Circ Res*, 2004;95:717–25.
85. Akar FG, Nass RD, Hahn S, et al., Dynamic changes in conduction velocity and gap junction properties during development of pacing-induced heart failure, *Am J Physiol Heart Circ Physiol*, 2007;293:H1223–30.
86. Dhein S, Hagen A, Jozwiak J, et al., Improving cardiac gap junction communication as a new antiarrhythmic mechanism: the action of antiarrhythmic peptides, *Naunyn Schmiedebergs Arch Pharmacol*, 2010;381:221–34.
87. Wetzel U, Boldt A, Lauschke J, et al., Expression of connexins 40 and 43 in human left atrium in atrial fibrillation of different aetiologies, *Heart*, 2005;91:166–70.
88. Nishida K, Michael G, Dobrev D, et al., Animal models for atrial fibrillation: clinical insights and scientific opportunities, *Europace*, 2010;12:160–72.
89. Ausma J, van der Velden HM, Lenders MH, et al., Reverse structural and gap-junctional remodeling after prolonged atrial fibrillation in the goat, *Circulation*, 2003;107:2051–8.
90. Firouzi M, Ramanna H, Kok B, et al., Association of human connexin40 gene polymorphisms with atrial vulnerability as a risk factor for idiopathic atrial fibrillation, *Circ Res*, 2004;95:e29–33.
91. Gollob MH, Jones DL, Krahn AD, et al., Somatic mutations in the connexin 40 gene (GJA5) in atrial fibrillation, *N Engl J Med*, 2006;354:2677–88.
92. Juang JM, Chern YR, Tsai CT, et al., The association of human connexin 40 genetic polymorphisms with atrial fibrillation, *Int J Cardiol*, 2007;116:107–12.
93. Nishida M, Kurose H, Roles of TRP channels in the development of cardiac hypertrophy, *Naunyn Schmiedebergs Arch Pharmacol*, 2008;378:395–406.
94. Watanabe H, Pathological role of TRP channels in cardiovascular and respiratory diseases, *Nippon Yakurigaku Zasshi*, 2009;134:127–30.
95. Van Wagoner DR, Voigt N, Bunnell B, et al., Transient receptor potential canonical (TRPC) channel subunit remodeling in clinical and experimental AF, *Heart Rhythm*, 2009;6:PO06–77.
96. Ellinor PT, Lunetta KL, Glazer NL, et al., Common variants in KCNN3 are associated with lone atrial fibrillation, *Nat Genet*, 2010;42:240–4.
97. Xu Y, Tuteja D, Zhang Z, et al., Molecular identification and functional roles of a Ca(2+)-activated K+ channel in human and mouse hearts, *J Biol Chem*, 2003;278:49085–94.
98. Ozgen N, Dun W, Sosunov EA, et al., Early electrical remodeling in rabbit pulmonary vein results from trafficking of intracellular SK2 channels to membrane sites, *Cardiovasc Res*, 2007;75:758–69.
99. Li N, Timofeyev V, Tuteja D, et al., Ablation of a Ca2+-activated K+ channel (SK2 channel) results in action potential prolongation in atrial myocytes and atrial fibrillation, *J Physiol*, 2009;587:1087–100.
100. Hove-Madsen L, Llach A, Bayes-Genis A, et al., Atrial fibrillation is associated with increased spontaneous calcium release from the sarcoplasmic reticulum in human atrial myocytes, *Circulation*, 2004;110:1358–63.
101. Vest JA, Wehrens XH, Reiken SR, et al., Defective cardiac ryanodine receptor regulation during atrial fibrillation, *Circulation*, 2005;111:2025–32.
102. Liang X, Xie H, Zhu PH, et al., Ryanodine receptor-mediated Ca2+ events in atrial myocytes of patients with atrial fibrillation, *Cardiology*, 2008;111:102–10.
103. Neef S, Dybkova N, Sossalla S, et al., CaMKII-dependent diastolic SR Ca2+ leak and elevated diastolic Ca2+ levels in right atrial myocardium of patients with atrial fibrillation, *Circ Res*, 2010:106(6):1134–44.
104. Voigt N, Traffords AW, Ravens U, et al., Increased diastolic sarcoplasmic reticulum calcium leak may contribute to arrhythmogenesis in patients with atrial fibrillation, *Cardiovasc Res*, 2010;87:S53.
105. Voigt N, Trafford AW, Ravens U, et al., Cellular and molecular determinants of altered atrial Ca2+ signaling in patients with chronic atrial fibrillation, *Circulation*, 2009;120:S667–8.
106. Dobrev D, Atrial Ca2+ signaling in atrial fibrillation as an antiarrhythmic drug target, *Naunyn Schmiedebergs Arch Pharmacol*, 2010;381:195–206.
107. Dobrev D, Teos LY, Lederer WJ, Unique atrial myocyte Ca2+ signaling, *J Mol Cell Cardiol*, 2009;46:448–51.
108. Wehrens XH, Lehnart SE, Reiken SR, et al., Ca2+/calmodulin-dependent protein kinase II phosphorylation regulates the cardiac ryanodine receptor, *Circ Res*, 2004;94:e61–70.
109. Sood S, Chelu MG, van Oort RJ, et al., Intracellular calcium leak due to FKBP12.6 deficiency in mice facilitates the inducibility of atrial fibrillation, *Heart Rhythm*, 2008;5:1047–54.
110. Lenaerts I, Bito V, Heinzel FR, et al., Ultrastructural and functional remodeling of the coupling between Ca2+ influx and sarcoplasmic reticulum Ca2+ release in right atrial myocytes from experimental persistent atrial fibrillation, *Circ Res*, 2009;105:876–85.
111. Li X, Zima AV, Sheikh F, et al., Endothelin-1-induced arrhythmogenic Ca2+ signaling is abolished in atrial myocytes of inositol-1,4,5-trisphosphate(IP3)-receptor type 2-deficient mice, *Circ Res*, 2005;96:1274–81.
112. Zhao ZH, Zhang HC, Xu Y, et al., Inositol-1,4,5-trisphosphate and ryanodine-dependent Ca2+ signaling in a chronic dog model of atrial fibrillation, *Cardiology*, 2007;107:269–76.
113. Nattel S, Atrial electrophysiological remodeling caused by rapid atrial activation: underlying mechanisms and clinical relevance to atrial fibrillation, *Cardiovasc Res*, 1999;42:298–308.
114. Fynn SP, Todd DM, Hobbs WJ, et al., Clinical evaluation of a policy of early repeated internal cardioversion for recurrence of atrial fibrillation, *J Cardiovasc Electrophysiol*, 2002;13:135–41.
115. Tse HF, Wang Q, Yu CM, et al., Time course of recovery of left atrial mechanical dysfunction after cardioversion of spontaneous atrial fibrillation with the implantable atrial defibrillator, *Am J Cardiol*, 2000;86:1023–5, A10.
116. Tse HF, Lau CP, Yu CM, et al., Effect of the implantable atrial defibrillator on the natural history of atrial fibrillation, *J Cardiovasc Electrophysiol*, 1999;10:1200–9.
117. Timmermans C, Lévy S, Ayers GM, et al., Spontaneous episodes of atrial fibrillation after implantation of the Metrix Atrioverter: observations on treated and nontreated

episodes. Metrix Investigators, *J Am Coll Cardiol*, 2000;35:1428–33.
118. Fareh S, Bénardeau A, Thibault B, et al., The T-type Ca(2+) channel blocker mibefradil prevents the development of a substrate for atrial fibrillation by tachycardia-induced atrial remodeling in dogs, *Circulation*, 1999;100:2191–7.
119. Shinagawa K, Shiroshita-Takeshita A, Schram G, et al., Effects of antiarrhythmic drugs on fibrillation in the remodeled atrium: insights into the mechanism of the superior efficacy of amiodarone, *Circulation*, 2003;107:1440–6.
120. Dobrev D, Cardiomyocyte Ca2+ overload in atrial tachycardia: is blockade of L-type Ca2+ channels a promising approach to prevent electrical remodeling and arrhythmogenesis?, *Naunyn Schmiedebergs Arch Pharmacol*, 2007;376:227–30.
121. Nishida K, Fujiki A, Sakamoto T, et al., Bepridil reverses atrial electrical remodeling and L-type calcium channel downregulation in a canine model of persistent atrial tachycardia, *J Cardiovasc Electrophysiol*, 2007;18:765–72.
122. Pandit SV, Berenfeld O, Anumonwo JM, et al., Ionic determinants of functional reentry in a 2-D model of human atrial cells during simulated chronic atrial fibrillation, *Biophys J*, 2005;88:3806–21.
123. Dobrev D, Wehrens XH, Calmodulin kinase II, sarcoplasmic reticulum Ca2+ leak, and atrial fibrillation, *Trends Cardiovasc Med*, 2010;20:30–4.
124. Neuman RB, Bloom HL, Shukrullah I, et al., Oxidative stress markers are associated with persistent atrial fibrillation, *Clin Chem*, 2007;53:1652–7.
125. Shiroshita-Takeshita A, Brundel BJ, Lavoie J, et al., Prednisone prevents atrial fibrillation promotion by atrial tachycardia remodeling in dogs, *Cardiovasc Res*, 2006;69:865–75.
126. Shiroshita-Takeshita A, Schram G, Lavoie J, et al., Effect of simvastatin and antioxidant vitamins on atrial fibrillation promotion by atrial-tachycardia remodeling in dogs, *Circulation*, 2004;110:2313–9.
127. Issac TT, Dokainish H, Lakkis NM, Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data, *J Am Coll Cardiol*, 2007;50:2021–8.
128. Dernellis J, Panaretou M, Relationship between C-reactive protein concentrations during glucocorticoid therapy and recurrent atrial fibrillation, *Eur Heart J*, 2004;25:1100–7.