Cellular bases for human atrial fibrillation

Antony J. Workman, PhD,* Kathleen A. Kane, PhD,† Andrew C. Rankin, MD*

From the *British Heart Foundation Glasgow Cardiovascular Research Centre, Faculty of Medicine, University of Glasgow, and †Strathclyde Institute of Pharmacy and Biomedical Sciences, Division of Physiology and Pharmacology, University of Strathclyde, Glasgow, United Kingdom.

Atrial fibrillation (AF) causes substantial morbidity and mortality. It may be triggered and sustained by either reentrant or nonreentrant electrical activity. Human atrial cellular refractory period is shortened in chronic AF, likely aiding reentry. The ionic and molecular mechanisms are not fully understood and may include increased inward rectifier K^+ current and altered Ca^{2+} handling. Heart failure, a major cause of AF, may involve arrhythmogenic atrial electrical remodeling, but the pattern is unclear in humans. Beta-blocker therapy prolongs atrial cell refractory period; a potentially antiarrhythmic influence, but the ionic and molecular mechanisms are unclear. The search for drugs to suppress AF without causing ventricular arrhythmias has been aided by basic studies of cellular mechanisms of AF. It remains to be seen whether such drugs will improve patient treatment.

Electrophysiological mechanisms of human atrial fibrillation and their study in single atrial cells

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It causes substantial morbidity and mortality. The majority of atrial premature beats that initiate AF originate from focal ectopic electrical activity in the pulmonary veins (PVs). AF is sustained by single- or multiple-circuit intra-atrial reentry and/or focal ectopy, and the latter may be reentrant or nonreentrant.[1] Nonreentrant mechanisms include abnormal automaticity (AA) and triggered activity. AA is the premature firing of action potentials (APs) because of abnormal diastolic membrane depolarisation (Figure 1A) and is favored by, for example, β-adrenergic stimulation or decreased vagal activity. Triggered activity is premature firing due to after-depolarizations. These may be early (EADs), occurring during repolarization and favored by AP prolongation, or delayed (DADs), occurring after an AP and favored by intracellular Ca^{2+} overload (Figure 1A). Reentry is rapid circuitous activation caused by unidirectional conduction block and favored by premature impulses, heterogeneity and shortening of the effective refractory period (ERP), and slowing of conduction velocity, θ (Figure 1B). Several electrophysiological parameters that may affect AF genesis and maintenance have been measured in human atrial isolated cells. The cellular ERP[2] and AP maximum upstroke velocity, V_{max} (Figure 1C), contribute to myocardial ERP and θ, respectively, so their reduction could promote reentry by shortening its wavelength, λ (Figure 1B). Cellular arrhythmic depolarizations (CADs[3]; Figure 1D) may represent AA, EADs, or DADs, with potential involvement in nonreentrant mechanisms.

Atrial cellular electrical remodeling in AF

Atrial myocardial electrical and mechanical activity and structure adapt, or remodel, in response to a variety of diseases and other stimuli. For example, congestive heart failure (CHF) may involve electrical remodeling, atrial dilation, and interstitial fibrosis, each potentially predisposing to AF. Once AF occurs, the rapid atrial rate causes atrial electrical remodeling that promotes AF, so AF is autoperpetuating. In goats, induced AF progressively shortened the atrial ERP and AF interval over 24 hours, which reduced the reentry λ and increased AF vulnerability.[4] Maximal ERP shortening may precede maximal AF duration, but the ERP shortening contributes to the AF substrate. In our laboratory, a similar ERP shortening was found in atrial cells isolated from patients with chronic AF (Figure 1C). This was associated with impaired ERP rate adaptation, shortening and triangulation of the AP and no change in V_{max}.[2] The shortened AP permitted full repolarization at the fast rates typically encountered in AF and thus prevented the depolarization of the maximum diastolic potential (MDP), that was observed in sinus rhythm (SR).[2] This effect on MDP might limit Ca^{2+} overload in the remodeled atrium, but the ERP changes favor reentry. The ERP is largely determined by the AP duration (APD), which depends on a delicate balance of inward and outward ion currents flowing through
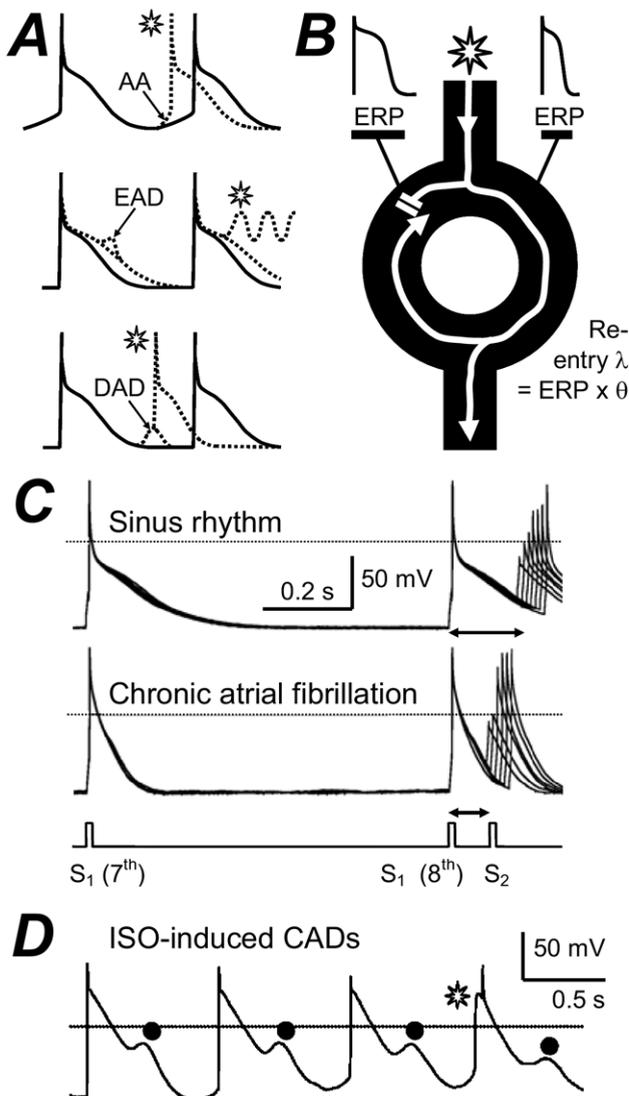
Figure 1 Electrophysiological mechanisms of arrhythmias and their study in human atrial cells. **A:** Representation of premature APs (*) from AA, EADs, or DADs. **B:** Premature impulse divides at functional or anatomical obstacle, blocks at tissue with normal (*left side*), but conducts with short (*right*) ERP and reenters previously inexcitable zone. λ = wavelength; θ = conduction velocity. **C:** Original APs stimulated in an atrial cell from a patient in SR or in AF by conditioning pulses (S_1) and premature test pulses (S_2). ERP ($\leftrightarrow$) = longest S_1-S_2 failing to produce S_2 response of amplitude >80% of S_1. **D:** Original APs stimulated by a pulse train in the presence of 0.05 μM isoproterenol (ISO), producing CADs (●). The * may represent AA. Panels C and D are based on data in references 2 and 3 with permission from Elsevier.

a variety of membrane protein channels, pumps, and exchangers. Therefore, an understanding of the mechanisms of human AF-induced atrial electrical remodeling requires knowledge about precise changes in each of these currents, and their contributions to the AP, in AF.

Potential ionic mechanisms of electrical remodeling in AF

Many human atrial ion currents have so far been studied in AF; they are shown in Table 1. The inward rectifier K^+

current (I_{K1}) is the main determinant of the resting potential (V_m). Other currents contribute, including acetylcholine-activated K^+ current (I_{KACh}), Na^+, K^+ pump current (I_p), and possibly ATP-sensitive K^+ current (I_{KATP}). I_{K1} and I_{KACh} also contribute to terminal repolarization. There is consensus that chronic AF is associated with increased density of I_{K1} (Table 1). Furthermore, despite decreased parasympathetic-regulated I_{KACh}, a constitutively active (CA) I_{KACh}, not requiring its endogenous agonist, is induced in AF (Figure 2). A single study on I_p, from our laboratory, showed no change in AF, and changes in I_{KATP} are variable. The reported increases in I_{K1} and CA I_{KACh} were most prominent (with enhanced inward current) at voltages more negative than the AP voltage range. However, enhanced outward I_{K1} has also been reported, within the AP voltage range,[5,6,8] which may contribute to the APD and ERP shortening in AF. Increased I_{K1} should also hyperpolarize V_m; while difficult to ascertain in human atrial isolated cells since the "chunk" isolation method may depolarize them, this has been reported in atrial trabeculae.[6] The AP fires when depolarization sufficient to drive V_m to threshold activates inward Na^+ current (I_{Na}), causing the regenerative and rapid AP upstroke; the larger I_{Na}, the faster V_{max}. A single study reported no change in I_{Na} density in AF, consistent with V_{max} (Table 1), although its inactivation voltage dependency was altered. Partial, or early, repolarization follows the AP upstroke, via activation of a transient outward K^+ current (I_{TO}) and the ultrarapid delayed rectifier K^+ current (I_{Kur}). AF consistently and markedly reduced I_{TO}, but data for I_{Kur} are equivocal (Table 1). The I_{TO} reduction may contribute to AP triangulation in AF, as shown by blocking I_{TO} with 4-aminopyridine (4-AP).[2] However, its contribution to the APD_{90} and ERP is unclear since 4-AP also blocks I_{Kur}, although mathematical modeling suggested a negligible role.[34] The AP plateau is maintained by inward, L-type Ca^{2+}, current (I_{CaL}), which is consistently and markedly reduced in chronic AF (Table 1), despite increased single-channel open probability.[35] Such I_{CaL} reduction depresses the AP plateau, consistent with acute effects of nifedipine[2] or simulated I_{CaL} reduction,[34] although its contribution alone to the shortening of the APD_{90}[2,34] or ERP[2] may be small. Mid/late repolarization results from activation of I_{Kur} as well as from the rapid (I_{Kr}) and slow (I_{KS}) delayed rectifiers, which are balanced by inward Na^+-Ca^{2+} exchange current ($I_{Na/Ca}$) following the $[Ca^{2+}]_i$ transient. $I_{Na/Ca}$ also underlies the transient inward current responsible for DADs. However, any role for these currents in human AF remodeling is presently unclear, since data are either equivocal or unavailable (Table 1). AA results from decreased outward and/or increased inward diastolic currents, including $I_{Na/Ca}$ and the "funny" current (I_f). However, data on I_f are also lacking.

Human PV isolated cell electrophysiology has not yet been studied. Chronic atrial tachypacing (AT) in dogs produced APD shortening in PV cells that was qualitatively similar to that in atrial cells and also produced similar

Table 1 Human atrial cellular electrophysiological changes associated with AF, ventricular dysfunction, and drug therapy

Human atrial cell electrophysiological measurement	Chronic AF	Post-CS AF	CHF, LVSD, and/or atrial dilation	Chronic β_1-blocker therapy
ERP	↓[2]	↔[22]	NDA	↑[3,22,31]
APD_{90}	↓[2,5–7]	↔[22]	↑[23,24] ↔[25,26]	↑[22,31]
APD_{50}	↔[2,6] ↑[7]	↔[22]	↔[23,24] ↓[26]	↔[3,31]
AP V_{max}	↔[2]	↔[22]	NDA	↔[31]
I_{K1}	↑[2,5,6,8–12]	↔[9,22]	↓[23] ↔*[27]	↓[32]
I_{KACh}	↑[5] ↓[6,9,10,12]	↔[9]	↓[23]	NDA
CA I_{KACh}	↑[10,12]	NDA	NDA	NDA
I_p	↔[13]	NDA	NDA	NDA
I_{KATP}	↓[14] ↑[15]	NDA	↔[24]	NDA
I_{Na}	↔[5]	NDA	NDA	NDA
I_{TO}	↓[2,5,8,16,17]	↔[22]	↑[26] ↓*[27,28]	↓[31,32]
I_{Kur} (I_{SUS})	↓[8,16] ↔[2,5,17]	↔[22]	↔[25,26] ↔*[28] ↓*[27]	↔[31,32]
I_{CaL}	↓[2,5,7,11,18–21]	↑[18] ↔[22]	↓[29] ↔[25,30] ↓*[27]	↔[3,7,22,31,33]
I_{CaL} % ↑ by β stimulation	↑[18–21]	↔[22]	↓[29,30]	↔[3,22]
I_{CaL} % ↑ by 5-HT	↑[7]	NDA	↓[29]	↑[7,33]
$I_{Na/Ca}$, $I_{Na/H}$, I_{Kr}, I_{Ks}, $I_{Cl(swell)}$, I_{CaB}, I_f	NDA	NDA	NDA	NDA

Arrows show direction of change relative to "controls."
*= atrial dilation only; NDA = no data available. See text for definitions.

changes in I_{K1}, I_{TO}, and I_{CaL}.[36] However, a current that may be analogous to human CA I_{KACh} was increased more strongly in PV cells than in atrial cells, perhaps favoring PV reentry.[37] The relative importance of reentrant versus non-reentrant activity to PV arrhythmogenesis, either before or after AF remodeling, is unknown.[1]

Atrial electrical activity is intricately linked with cellular and subcellular Ca^{2+} fluxes, particularly via $I_{Na/Ca}$. Intracellular Ca^{2+} handling is altered in AF, although human data are sparse. In canine atrial cells, acute AT, analogous to a paroxysm of AF, abruptly increases diastolic $[Ca^{2+}]_i$, a potential trigger of the remodeling process. Chronic AT, by contrast, markedly decreased the $[Ca^{2+}]_i$ transient amplitude,[38] perhaps reflecting protection from $[Ca^{2+}]_i$ overload. This may result from a deficient trigger function of the markedly reduced I_{CaL}, since sarcoplasmic reticular Ca^{2+} content was preserved.[38] Human AF was associated with a potentially arrhythmogenic increase in the frequency of Ca^{2+} sparks and waves.[39] This may represent sarcoplasmic reticular Ca^{2+} leak due to ryanodine receptor hyperphosphorylation.[40]

Whether the combined ionic changes so far established in human AF can account for the associated AP changes is unclear and will require the aid of mathematical models. One such model suggested that the combined I_{K1}, I_{TO}, and I_{CaL} changes could explain the AP changes,[34] although in the dog, concurrent $[Ca^{2+}]_i$ changes were required.[38] Another model suggested a major contribution from the I_{K1} increase to the stabilization of reentry.[41]

Potential molecular mechanisms in AF: Genetic and nongenetic

Many atrial ion current changes in human AF are accompanied by, and often considered to be caused by, altered tissue expression of the ion channel pore-forming α-subunits that carry them, for example, increased Kir2.1 (carries I_{K1}) and decreased Kv4.3 (I_{TO}).[11] However, there are some intriguing and controversial exceptions. Protein levels of I_{CaL} α-subunits were decreased by 40%–55% in three studies,[35,42,43] in line with I_{CaL} reduction, but were unchanged in four others.[11,20,21,44] Also, despite increased CA I_{KACh} in AF (Table 1), the Kir 3.1 protein level was decreased.[43] The apparent discrepancies between changes in ion current density and protein expression suggest post-translational modification or altered channel regulation. The magnitude of I_{CaL} is influenced by a balance between channel phosphorylation by kinases and dephosphorylation by phosphatases. Chronic AF upregulated phosphatase type-2A-C, reducing I_{CaL} without requiring reduced channel protein.[20] Similarly, induction of CA I_{KACh} in human AF resulted from abnormal protein kinase- (PK-) C function[12] (Figure 2C).

AF may be a heritable disorder: positive family history was identified in 5% of patients with AF.[45] Several genetic mutations have been associated with familial AF, mainly for K^+ channels. Most are gain-of-function mutations, increasing I_{Ks}, I_{Kr}, or I_{K1} and expected to shorten ERP and promote reentry, although an I_{Kur} loss-of-function mutation might prolong ERP.[45] However, such mutations occur in other diseases, for example, dilated cardiomyopathy and long-QT, short-QT, and Brugada syndromes, some of which are comorbidities for AF. Nevertheless, it seems that genetic variants are involved in the pathogenesis of AF in a proportion of cases.

Neurohumoral involvement in AF

AF can result from a sympathetic/parasympathetic imbalance. Furthermore, neurohumoral activation in CHF, an important cause of AF, increases circulating levels of catecholamines, angiotensin, and endothelin (ET-1). Beta-adrenergic stimulation from catecholamines may promote DADs, by increasing I_{CaL} and Ca^{2+}-induced Ca^{2+} release. AF remodeling potentiated the relative increase in I_{CaL}

A
□ Sinus rhythm

Chronic atrial fibrillation

2 pA
0.2 s

I_{K1} CA I_{KACh}

B

Channel open probability (%)

15

10

5

0.2
0

I_{K1} CA I_{KACh}

C
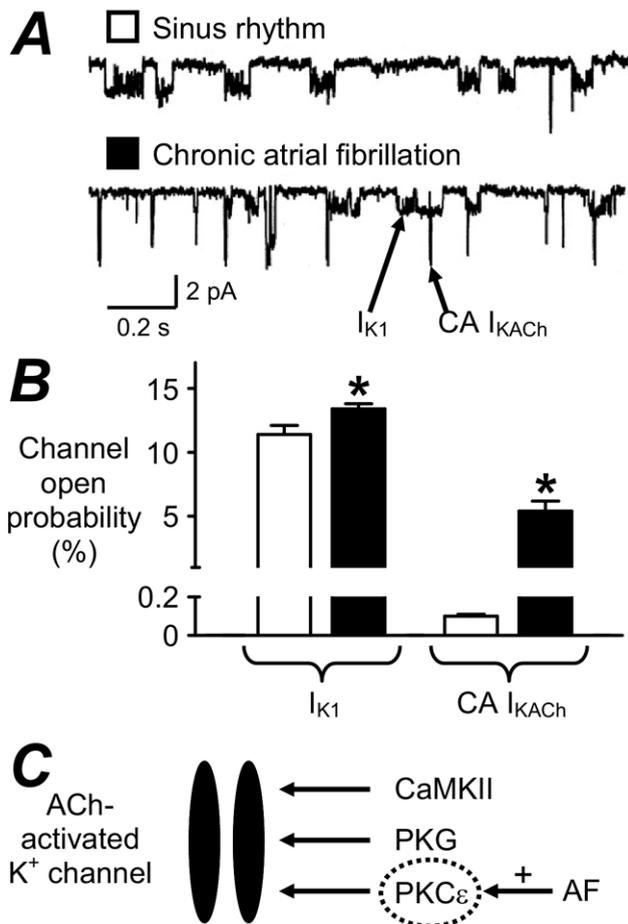ACh-activated K^+ channel

CaMKII
PKG
PKCε ← + AF

Figure 2 Induction of constitutively active acetylcholine-activated K^+ current, CA I_{KACh}, in human AF. Single-channel I_{K1} and CA I_{KACh} currents (**A**) and mean (±standard error) open probabilities (**B**), recorded at −120 mV in atrial cells from patients in SR (open symbols) and AF (solid symbols). *P <.05 versus SR. **C**: Potential signaling mechanism of increased CA I_{KACh} in AF. In SR, I_{KACh} may require channel phosphorylation by calmodulin-dependent PK II (CaMKII), PKG, and PKC.[12] In AF, CA I_{KACh} may result from upregulation of PKCε.[12] Panels A and B are based on data in reference 10 with permission from Lippincott Williams & Wilkins.

produced by β-stimulation (Table 1). We demonstrated that ET-1 had no direct effect on I_{CaL}, APD, or ERP in human atrial cells. However, it abolished isoproterenol-induced increases in I_{CaL}, APD_{50}, and CADs (Figure 1D), with no effect on ERP.[3] Thus, ET-1 might exert an antiadrenergic antiarrhythmic influence in the atria of patients with CHF. Serotonin (5-HT) is released from platelets aggregating in static blood in fibrillating atria. We demonstrated that 5-HT may be arrhythmogenic in human atrium, by increasing I_{CaL} and producing CADs, without affecting ERP.[33] Atrial remodeling by AF may protect from these effects, however, since they were attenuated in cells from patients with chronic AF[7] (Table 1).

Postoperative AF: Is there a predisposing atrial cellular electrophysiological substrate?
AF is common in patients after cardiac surgery (CS). Post-CS AF is independently predicted by old age, pre-CS AF, and pre-CS P-wave changes. Therefore, pre-CS atrial cellular electrophysiology could influence the propensity for new-onset AF post-CS, which is an issue presently under debate. An early study showed an association between post-CS AF and an enhanced pre-CS I_{CaL},[18] potentially arrhythmogenic post-CS, when catecholamines are elevated. However, we recently demonstrated, by contrast, that pre-CS I_{CaL}, AP parameters, or ERP were not predictive of post-CS AF.[22] Furthermore, no other ion current that was measured, nor the I_{CaL} response to β-stimulation, was different between patients with and without post-CS AF (Table 1). Some currents remain to be studied, but it appears that the electrically remodeled state caused by chronic AF (Table 1) is not present pre-CS in the atrial cells of patients who develop new-onset post-CS AF.

Heart failure–induced atrial remodeling
AF is common in patients with CHF, and left ventricular systolic dysfunction (LVSD) substantially increases the risk of AF. It is unclear whether atrial cellular electrical remodeling, in patients in SR, contributes to this predisposition to AF. The available human data are scarce and inconsistent (Table 1) and are compounded by inevitable variability in the patients' disease states and drug treatments. Atrial cellular electrical remodeling has been demonstrated in canine models of chronic ventricular tachypacing (VTP)-induced CHF. AF was invariably promoted, but the remodeling pattern differed from AF: atrial ERP was unchanged or increased, I_{K1} was not increased, both I_{TO} and I_{KS} were decreased, I_{CaL} was only moderately decreased, and $I_{Na/Ca}$ was increased.[46,47] The increased $I_{Na/Ca}$ might favor a triggered origin of AF in this model. CHF also caused atrial fibrosis, and while the ionic remodeling reversed after ceasing VTP, the fibrosis and AF persistence did not.[46] Thus, atrial electrical remodeling may contribute to AF genesis but was not necessary for its maintenance in this model. Human CHF or LVSD were associated with variable changes in APD, and cellular ERP has not been studied (Table 1). Human atrial ionic changes in CHF or LVSD may be expected to differ from those in chronic AF, with decreased I_{K1} and increased I_{TO}, decreased or unchanged I_{CaL}, and a decreased I_{CaL} response to β-stimulation so far reported (Table 1). The pattern may depend on the degree of atrial dilation, which itself may cause ionic remodeling (Table 1). Moreover, CHF- and AF-induced atrial remodeling interact. In dogs, this interaction was complex, not cumulative: chronic AT, imposed on a CHF-remodeled atrium, caused moderate ERP shortening, I_{K1} increase, and I_{CaL} decrease but did not further remodel I_{TO}, I_{KS}, or $I_{Na/Ca}$.[47] No comparative human atrial data could be found.

Atrial remodeling by chronic drug therapy
Atrial electrophysiology remodels in response not only to diseases and aging but also to long-term drug treatments; so-called pharmacological remodeling.[31] This was originally demonstrated in rabbits: treatment with the β_1-blocker metoprolol caused an adaptational prolongation of the atrial
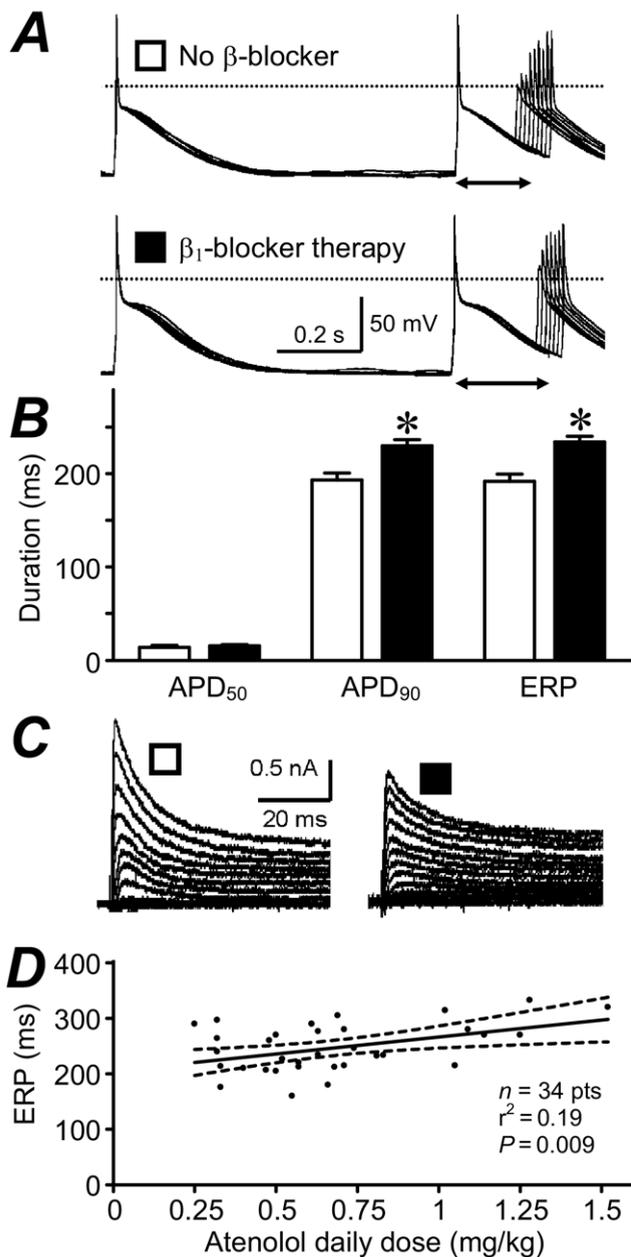
Figure 3 Pharmacological remodeling of human atrial cell electrophysiology by β_1-blocker therapy. **A:** APs and ERP (↔); **B:** mean (±standard error) APD at 50% and 90% repolarization (APD$_{50}$ and APD$_{90}$) and ERP; **C:** transient outward K$^+$ currents, recorded in single atrial myocytes from patients in SR, treated with a β_1-blocker ≥7 days (solid symbols) versus those in SR who were not treated with a β-blocker (open symbols). *P <.05 versus non β-blocker. **D:** Correlation between atrial cell ERP and patient's atenolol dose/body weight. Heart rate ≤75 bpm. *Dashed lines* indicate the 95% confidence interval. Panels A and C are based on data in reference 31 with permission from Elsevier.

APD, maximally after 6 days.[48] Beta-blockers are increasingly used to treat AF and HF. We demonstrated that in patients in SR, β_1-blocker treatment for ≥7 days was independently associated with prolonged atrial cell APD$_{90}$ and ERP[22,31] (Figure 3A, 3B), and not with I$_{CaL}$.[22] The I$_{TO}$ was reduced (Figure 3C), and I$_{SUS}$ was unchanged (Table 1). Preliminary data from our group suggest that the I$_{TO}$ reduc-

tion does not involve altered voltage dependency or kinetics[32] or altered ion channel expression[49] and that I$_{K1}$ is also reduced.[32] Recent subgroup analysis revealed a significant correlation between ERP and atenolol dose (Figure 3D), suggesting that the ERP prolongation is at least partly caused, directly or indirectly, by the atenolol treatment. Such ERP prolongation might contribute to the antiarrhythmic effects of beta-blockers, although a potentiation by chronic β-blockade of effects of 5-HT on I$_{CaL}$ (Table 1) and CADs[33] could also oppose them.

How research on cellular bases for human AF is driving new therapeutic strategies

Traditional ERP-prolonging drugs, which are used to inhibit reentry, act by blocking I$_{Kr}$. This is problematic because I$_{Kr}$ exists in the ventricle as well as atrium, which risks ventricular EADs and fibrillation. I$_{Kur}$ and I$_{KACh}$ are considered to be atrium specific, so their block might prolong ERP in atrium only, depending on secondary ionic effects. However, targeting ion channel regulation may be preferable to ion channel block. Altering the PKC pathway that induces CA I$_{KACh}$ in chronic AF[12] might avoid undesirable effects of inhibiting parasympathetic-regulated I$_{KACh}$ on sinoatrial node and bladder. Blocking the phosphatase-induced I$_{CaL}$ decrease caused by AF[20] is another possibility. Moreover, "de-remodeling," in theory, might be better than such "anti-remodeling" since blocking potentially protective adaptations may be risky. Pharmacological targeting of nonreentrant mechanisms of AF also may be considered.

AF is a highly complex, multifactorial, and dynamic disorder with differing characteristics and etiologies among individuals. As such, it presents an enormous challenge for the development of drugs for its effective and safe treatment. Current basic research is driving the search for new drugs. Several drugs, including I$_{Kur}$ and I$_{KACh}$ blockers, are entering clinical trials. It remains to be seen whether they will improve patient treatment.

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