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Cellular bases for human atrial fibrillation

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Abstract.

Atrial fibrillation (AF) causes substantial morbidity and mortality. It may be triggered and sustained by either re-entrant or non-re-entrant electrical activity. Human atrial cellular refractory period is shortened in chronic AF, likely aiding re-entry. 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 remodelling, but the pattern is unclear in humans. Beta-blocker therapy prolongs atrial cell refractory period; a potentially anti-arrhythmic 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.

Keywords: Atrial fibrillation; Arrhythmias (mechanisms); Refractory period; Transmembrane action potential; Ion current; Heart failure; Beta-blocker; Electrical remodelling.

List of abbreviations.

4-AP (4-aminopyridine); 5-HT (5-hydroxytryptamine/serotonin); AA (abnormal automaticity); AF (atrial fibrillation); AP (action potential); APD (action potential duration); APD₅₀ (action potential duration at 50% repolarisation); AT (atrial tachypacing); CA (constitutively active); CAD (cellular arrhythmic depolarisation); CHF (congestive heart failure); CS (cardiac surgery); DAD (delayed afterdepolarisation); EAD (early afterdepolarisation); ERP (effective refractory period); ET-1 (endothelin); I_{CaL} (L-type Ca^{2+} current); I_f (funny current); I_{K1} (inward rectifier K^+ current); I_{KACH} (acetylcholine-activated K^+ current); I_{KATP} (adenosine triphosphate-sensitive K^+ current); I_{Kr} (rapid delayed rectifier K^+ current); I_{Ks} (slow delayed rectifier K^+ current); I_{Kur} (ultra-rapid delayed rectifier K^+ current); I_{Na} (Na^+ current); $I_{Na/Ca}$ (Na^+ - Ca^{2+} exchange current); I_p (Na^+ , K^+ pump current); ISO (isoproterenol); I_{TO} (transient outward K^+ current); LVSD (left ventricular systolic dysfunction); MDP (maximum diastolic potential); NDA (no data available); PK (protein kinase); PV (pulmonary vein); SR (sinus rhythm); V_m (resting potential); V_{max} (maximum upstroke velocity); VTP (ventricular tachypacing); λ (wavelength); θ (conduction velocity).

Electrophysiological mechanisms of human AF, 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 (PV). AF is sustained by single or multiple circuit intra-atrial re-entry and/or focal ectopy, and the latter may be re-entrant or non-re-entrant.¹ Non-re-entrant mechanisms include abnormal automaticity (AA) and triggered activity. Abnormal automaticity is the premature firing of action potentials (AP) due to abnormal diastolic membrane depolarisation (Fig 1A), and is favoured by, e.g., β -adrenergic stimulation or decreased vagal activity. Triggered activity is premature firing due to afterdepolarisations. These may be early (EAD), occurring during repolarisation and favoured by AP-prolongation, or delayed (DAD), occurring after an AP and favoured by intracellular Ca^{2+} -overload (Fig 1A). Re-entry is rapid circuitous activation caused by unidirectional conduction block, and favoured by premature impulses, heterogeneity and shortening of effective refractory period (ERP), and slowing of conduction velocity, θ (Fig 1B). Several electrophysiological parameters which may affect AF genesis and maintenance have been measured in human atrial isolated cells. The cellular ERP² and AP maximum upstroke velocity, V_{\max} (Fig 1C) contribute to myocardial ERP and θ , respectively, so their reduction could promote re-entry by shortening its wavelength, λ (Fig 1B). “Cellular arrhythmic depolarisations”, CADs³ (Fig 1D) may represent AA, EADs or DADs, with potential involvement in non-re-entrant mechanisms.

Atrial cellular electrical remodelling 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 remodelling, atrial dilation and interstitial fibrosis, each potentially predisposing to AF. Once AF occurs, the rapid atrial rate causes atrial electrical remodelling which promotes AF, so AF is auto-perpetuating. In goats, induced AF progressively shortened atrial ERP and AF-interval over 24 hr, which reduced the re-entry 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 (Fig 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 repolarisation at the fast rates typically encountered in AF, and thus prevented the depolarisation of the maximum diastolic potential (MDP) which was observed in sinus rhythm (SR).² This effect on MDP might limit Ca^{2+} -overload in the remodelled atrium, but the ERP changes favour re-entry. The ERP is largely determined by the AP duration (APD), which depends on a delicate balance of inward and outward ion currents flowing through a variety of membrane protein channels, pumps and exchangers. Therefore, an understanding of the mechanisms of human AF-induced atrial electrical remodelling requires knowledge about precise changes in each of these currents, and their contributions to the AP, in AF.

Potential ionic mechanisms of electrical remodelling in AF.

Many human atrial ion currents have so far been studied in AF; collated in the Table. 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 repolarisation. There is consensus that chronic AF is associated with increased density of I_{K1} (Table). Furthermore, despite decreased parasympathetic-regulated I_{KACH} , a constitutively active (CA) I_{KACH} , not requiring its endogenous agonist, is induced in AF (Fig 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 hyperpolarise V_m ; whilst difficult to ascertain in human atrial isolated cells since the “chunk” isolation method may depolarise them, this has been reported in atrial trabeculae.⁶ The AP fires when depolarisation 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), though its inactivation voltage-dependency was altered. Partial, or early, repolarisation

follows the AP upstroke, via activation of a transient outward K^+ current (I_{TO}) and the ultra-rapid delayed rectifier K^+ current (I_{Kur}). AF consistently and markedly reduced I_{TO} , but data for I_{Kur} are equivocal (Table). 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} , though mathematical modelling 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), despite increased single channel open probability.³⁵ Such I_{CaL} reduction depresses the AP plateau, consistent with acute effects of nifedipine² or simulated I_{CaL} reduction,³⁴ though its contribution, alone, to the APD_{90} ^{2,34}- or ERP²- shortening may be small. Mid/late repolarisation results from activation of I_{Kur} , as well as the rapid (I_{Kr}) and slow (I_{KS}) delayed rectifiers, 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-remodelling is presently unclear, since data are either equivocal or unavailable (Table). Abnormal automaticity 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 qualitatively similar APD-shortening in PV cells to atrial cells, and also similar changes in I_{K1} , I_{TO} and I_{CaL} .³⁶ However, a current which may be analogous to human CA I_{KACH} was increased more strongly in PV than atrial cells, perhaps favouring PV re-entry.³⁷ The relative importance of re-entrant versus non-re-entrant activity to PV arrhythmogenesis, either before or after AF-remodelling, is unknown.¹

Atrial electrical activity is intricately linked with cellular and sub-cellular Ca^{2+} fluxes, particularly via $I_{Na/Ca}$. Intracellular Ca^{2+} -handling is altered in AF, though 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 remodelling 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

Ca²⁺ sparks and waves.³⁹ This may represent sarcoplasmic reticular Ca²⁺ 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 though in dog, concurrent [Ca²⁺]_i changes were required.³⁸ Another suggested a major contribution from the I_{K1} increase to the stabilisation of re-entry.⁴¹

Potential molecular mechanisms in AF: genetic and non-genetic.

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; e.g., 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 unchanged in four others.^{11,20,21,44} Also, despite increased CA I_{KACH} in AF (Table), 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 de-phosphorylation 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 C function.¹² (Fig 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”, increasing I_{Ks}, I_{Kr} or I_{K1} and expected to shorten ERP and promote re-entry, though an I_{Kur} loss of function mutation might prolong ERP.⁴⁵ However, such mutations occur in other diseases, e.g., dilated cardiomyopathy, long-QT, short-QT and Brugada syndromes, some of which are co-morbidities 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-remodelling potentiated the relative increase in I_{CaL} produced by β -stimulation (Table). 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} , APD₅₀ and CADs (Fig 1D), with no effect on ERP.³ Thus, ET-1 might exert an anti-adrenergic anti-arrhythmic 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 remodelling by AF may protect from these effects, however, since they were attenuated in cells from patients with chronic AF⁷ (Table).

Post-operative AF: is there a predisposing atrial cellular electrophysiological substrate?

AF is common in patients following 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; 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 neither pre-CS I_{CaL} , AP parameters or ERP were predictive of post-CS AF.²² Furthermore, no other ion current measured, nor the I_{CaL} response to β -stimulation, were different between patients with and without post-CS AF (Table). Some currents remain to be studied, but it appears that the electrically remodelled state caused by chronic AF (Table) is not present pre-CS in the atrial cells of patients who develop new onset post-CS AF.

Heart failure-induced atrial remodelling.

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 remodelling, in patients in SR, contributes to this predisposition to AF. The available human data are scarce and inconsistent (Table), and compounded by inevitable variability in patients' disease states and drug treatments. Atrial cellular electrical remodelling has been demonstrated in canine models of chronic ventricular tachypacing (VTP)-induced CHF. AF was invariably promoted, but the remodelling 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 favour a triggered origin of AF in this model. CHF also caused atrial fibrosis, and whilst the ionic remodelling reversed after ceasing VTP, the fibrosis and AF persistence did not.⁴⁶ Thus, atrial electrical remodelling 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). 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). The pattern may depend on the degree of atrial dilation, which itself may cause ionic remodelling (Table). Moreover, CHF- and AF-induced atrial remodelling interact. In dogs, this interaction was complex, not summative: chronic AT, imposed on a CHF-remodelled 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 remodelling by chronic drug therapy.

Atrial electrophysiology remodels in response not only to diseases and ageing, but also to long-term drug treatments; so called "pharmacological remodelling".³¹ This was originally demonstrated in rabbits: treatment with the β_1 -blocker metoprolol caused an adaptational prolongation of the atrial 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 APD₉₀ and ERP^{22,31} (Fig 3A&B), and not with I_{CaL}.²² The I_{TO} was reduced (Fig 3C), and I_{SUS} was unchanged (Table). Preliminary data from our group suggest that the I_{TO} reduction does not involve altered voltage-dependency or kinetics,³² nor altered ion channel expression,⁴⁹ and that I_{K1} is also reduced.³² Recent sub-group analysis revealed a significant correlation between ERP and atenolol dose (Fig 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 anti-arrhythmic effects of beta-blockers, though a potentiation by chronic β -blockade of effects of 5-HT on I_{CaL} (Table) and CADs³³ could also oppose them.

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

Traditional ERP-prolonging drugs, to inhibit re-entry, do so by blocking I_{Kr}. This is problematic because I_{Kr} exists in ventricle as well as atrium, risking 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 which induces CA I_{KACH} in chronic AF¹² might avoid undesirable effects of inhibiting parasympathetic-regulated I_{KACH} on sinoatrial node and bladder. Blocking the phosphatase-induced I_{CaL} decrease caused by AF²⁰ is another possibility. Moreover, “de-remodelling”, in theory might be better than such “anti-remodelling”, since blocking potentially protective adaptations may be risky. Pharmacological targeting of non-re-entrant mechanisms of AF also may be considered.

AF is a highly complex, multifactorial and dynamic disorder with differing characteristics and aetiologies 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, 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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Table and Figure legends.

Table.

Human atrial cellular electrophysiological changes associated with AF, ventricular dysfunction and drug therapy. Arrows show direction of change relative to “controls”. *=atrial dilation only. NDA=no data available. See text for definitions.

Figure 1.

Electrophysiological mechanisms of arrhythmias and their study in human atrial cells. *A*, Representation of premature action potentials (*) from abnormal automaticity (AA), early (EAD) or delayed (DAD) afterdepolarisations. *B*, Premature impulse divides at functional or anatomical obstacle, blocks at tissue with normal (left side) but conducts with short (right) ERP, and re-enters previously inexcitable zone. λ =wavelength. θ =conduction velocity. *C*, Original APs stimulated in an atrial cell from a patient in SR, and 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 μ M isoproterenol (ISO), producing “cellular arrhythmic depolarisations”, CADs (\bullet). * may represent AA. *C&D* based on data in^{2&3} with permission from Elsevier.

Figure 2.

Induction of constitutively active acetylcholine-activated K^+ current, CA $I_{K_{ACh}}$, in human AF. Single channel I_{K1} and CA $I_{K_{ACh}}$ currents (*A*) and mean (\pm SE) open probabilities (*B*), recorded at -120 mV in atrial cells from patients in SR (\square) and AF (\blacksquare). *= $P<0.05$ vs SR. *C*, Potential signalling mechanism of increased CA $I_{K_{ACh}}$ in AF. In SR, $I_{K_{ACh}}$ may require channel phosphorylation by calmodulin-dependent protein kinase (PK) II (CaMKII), PKG and PKC.¹² In AF, CA $I_{K_{ACh}}$ may result from upregulation of PKC ϵ .¹² *A&B* based on data in¹⁰ with permission from Lippincott Williams & Wilkins.

Figure 3.

“Pharmacological remodelling” of human atrial cell electrophysiology by β_1 -blocker therapy. *A*, Action potentials and ERP (\leftrightarrow); *B*, mean (\pm SE) AP duration at 50 and 90% repolarisation (APD₅₀ & APD₉₀) and ERP; *C*, transient outward K⁺ currents, recorded in single atrial myocytes from patients in SR, treated with a β_1 -blocker ≥ 7 days (■) *vs* those in SR, not treated with a β -blocker (□). $\ast = P < 0.05$ *vs* □. *D*, Correlation between atrial cell ERP and patient’s atenolol dose/body weight. Heart rate ≤ 75 beats/min. Dashed lines: 95% confidence interval. *A* & *C* based on data in³¹ with permission from Elsevier.

Table.

Human atrial cell electro-physiological measurement	Chronic AF	Post-cardiac surgery AF	CHF, LVSD and/or atrial dilation	Chronic β_1 -blocker therapy
ERP	\downarrow^2	\leftrightarrow^{22}	NDA	$\uparrow^{3,22,31}$
APD ₉₀	$\downarrow^{2,5-7}$	\leftrightarrow^{22}	$\uparrow^{23,24} \leftrightarrow^{25,26}$	$\uparrow^{22,31}$
APD ₅₀	$\leftrightarrow^{2,6} \uparrow^7$	\leftrightarrow^{22}	$\leftrightarrow^{23,24} \downarrow^{26}$	$\leftrightarrow^{3,31}$
AP V _{max}	\leftrightarrow^2	\leftrightarrow^{22}	NDA	\leftrightarrow^{31}
I _{K1}	$\uparrow^{2,5,6,8-12}$	$\leftrightarrow^{9,22}$	$\downarrow^{23} \leftrightarrow^{*27}$	\downarrow^{32}
I _{KACH}	$\uparrow^5 \downarrow^{6,9,10,12}$	\leftrightarrow^9	\downarrow^{23}	NDA
CA I _{KACH}	$\uparrow^{10,12}$	NDA	NDA	NDA
I _p	\leftrightarrow^{13}	NDA	NDA	NDA
I _{KATP}	$\downarrow^{14} \uparrow^{15}$	NDA	\leftrightarrow^{24}	NDA
I _{Na}	\leftrightarrow^5	NDA	NDA	NDA
I _{TO}	$\downarrow^{2,5,8,16,17}$	\leftrightarrow^{22}	$\uparrow^{26} \downarrow^{*27,28}$	$\downarrow^{31,32}$
I _{Kur} (I _{SUS})	$\downarrow^{8,16} \leftrightarrow^{2,5,17}$	\leftrightarrow^{22}	$\leftrightarrow^{25,26} \leftrightarrow^{*28} \downarrow^{*27}$	$\leftrightarrow^{31,32}$
I _{CaL}	$\downarrow^{2,5,7,11,18-21}$	$\uparrow^{18} \leftrightarrow^{22}$	$\downarrow^{29} \leftrightarrow^{25,30} \downarrow^{*27}$	$\leftrightarrow^{3,7,22,31,33}$
I _{CaL} % \uparrow by β -stim	\uparrow^{18-21}	\leftrightarrow^{22}	$\downarrow^{29,30}$	$\leftrightarrow^{3,22}$
I _{CaL} % \uparrow by 5-HT	\downarrow^7	NDA	\downarrow^{29}	$\uparrow^{7,33}$
I _{Na/Ca} , I _{Na/H} , I _{Kr} , I _{Ks} , I _{Cl(swell)} , I _{CaB} , I _f	NDA	NDA	NDA	NDA

Figure 1

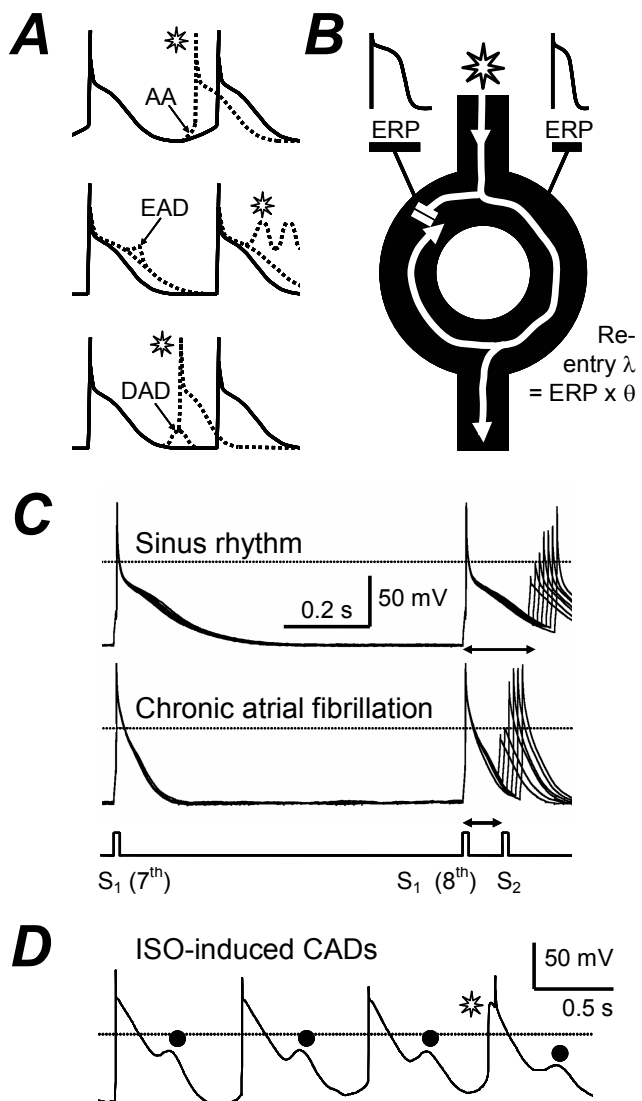


Figure 2

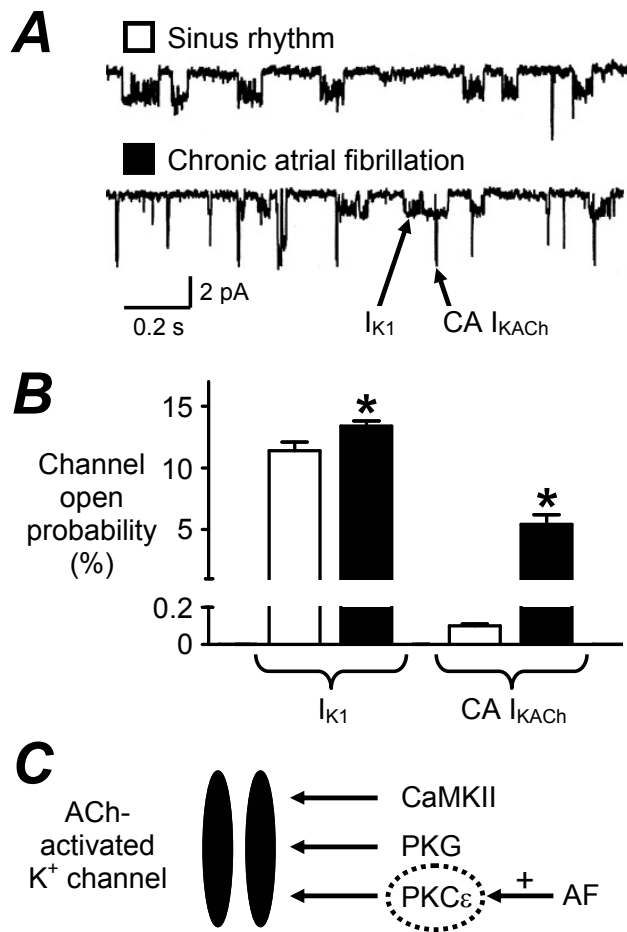


Figure 3

