

# Role of up-regulation of $I_{K1}$ in action potential shortening associated with atrial fibrillation in humans

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Received 6 August 2004; received in revised form 24 January 2005; accepted 25 January 2005

Available online 24 February 2005

Time for primary review 23 days

## Abstract

**Objectives:** Although previous studies in dogs have indicated a minimal role for changes in  $I_{K1}$  in the shortening of action potential duration (APD) associated with atrial fibrillation (AF), in humans, there is evidence for significant AF-induced up-regulation of this current. In this computer model study, we investigated the relative contributions of the remodeling of  $I_{K1}$ , L-type calcium current, and other remodeled ionic channel currents to AF-induced APD reduction in human atrium.

**Methods:** Two computer models of electrical activity of human atrial cell were modified by incorporating experimental data of AF-induced changes in human atrial ionic channel conductance and kinetics reported by Bosch et al. ( $I_{CaL}$ ,  $I_{to}$ ,  $I_{K1}$ , and  $I_{Na}$ ) (AF-1) and Workman et al. ( $I_{CaL}$ ,  $I_{to}$ , and  $I_{K1}$ ) (AF-2). The roles and relative importance of individually remodeled ion channels in the APD reduction in human atrium were evaluated by the removal and exclusive methods, in which remodeling of specific currents was omitted, or considered in isolation, in the two models.

**Results:** When tested together, previously reported AF-induced changes in sarcolemmal ion currents result in marked shortening of atrial APD<sub>90</sub>. With the AF-1 remodeled parameters, there is a 62% reduction in APD<sub>90</sub> for the Nygren et al. model, and a 68% reduction for the Courtemanche et al. model, which are comparable to experimental results of 60% reduction seen in humans. When tested individually, AF-1-induced changes in  $I_{CaL}$ ,  $I_{K1}$ , or  $I_{to}$  alone result in APD<sub>90</sub> reduction of 20%, 64%, and –10%, respectively, for the Nygren et al. model, and 27%, 40%, and 11.6%, respectively, for the Courtemanche et al. model. With the AF-2 remodeled parameters, there is a 47% reduction in APD<sub>90</sub> for the Nygren et al. model and a 49% reduction for the Courtemanche et al. model, which are also comparable to experimental results of 45% reduction. When tested individually, AF-2-induced changes in  $I_{CaL}$  or  $I_{K1}$  alone result in APD<sub>90</sub> reduction of 20% and 40%, respectively, for the Nygren et al. model, and 14% and 21%, respectively, for the Courtemanche et al. model.

**Conclusion:** Previously reported changes in L-type  $Ca^{2+}$  current are insufficient to account for the observed reduction in atrial APD associated with persistent AF. Up-regulation of  $I_{K1}$  has a greater influence on atrial APD in the human model.

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**Keywords:** Human atrial fibrillation; Remodeling; Mathematical modeling

## 1. Introduction

Changes in action potentials of atrial myocytes induced by chronic atrial fibrillation (AF) have been described in

various animal models [1,2] and in humans [3–5]. The predominant change is action potential duration (APD) shortening and it is believed that this is one mechanism contributing to the self-perpetuation of AF [1] as it encourages the initiation and maintenance of multiple reentrant wavelets in a limited mass of atrial tissue [6].

Experimental work on the mechanism of this AF-induced shortening of APD has focused on the canine

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model [2,7,8] and has demonstrated that the predominant cause of this shortening is a down-regulation of  $I_{CaL}$  current density, with little or no change in  $I_{K1}$ ,  $I_{Kr}$ ,  $I_{Ks}$ ,  $I_{CaT}$ , or  $I_{Cl,Ca}$  [7]. In humans, however, AF-induced changes are more complex and include up-regulation of  $I_{K1}$  current density, down-regulation of  $I_{CaL}$  and  $I_{to}$  current densities, and changes in the kinetics of  $I_{to}$ ,  $I_{CaL}$ , and  $I_{Na}$  channels [3–5]. As a consequence, it is possible that the ionic mechanisms involved in the AF-induced APD reduction are different in humans. We used computer modeling techniques to determine (1) whether the AF-induced changes in ion channel currents were sufficient to account for the observed changes in the APD reduction seen in humans, and (2) the relative contribution of different ion channel current changes to the reduction in overall APD, especially the relative contribution of AF induced changes in  $I_{K1}$  and  $I_{CaL}$ .

## 2. Methods

Two models of electrical activity of human atrial myocytes, developed by Nygren et al. [9] and Courtemanche et al. [10], were modified to incorporate experimental data of AF-induced changes in ion channel conductance and kinetics. The two models were based on very similar data, but assumed different baseline action potential (AP) and therefore magnitudes of the underlying ionic currents—a triangle AP for the Nygren et al. model and the spike-and-dome AP for the Courtemanche et al. model. Such different AP profiles reflect the heterogeneous nature of human atrial electrophysiology. Although there are differences in the maximal conductances of some of the rectifier potassium currents, most ion channel kinetics and conductances are similar in the two models. By adjusting some ion current densities ( $I_{sus}$  reduced by 60%,  $I_{to}$  increased by 100%,  $I_{CaL}$  increased by 33%, and  $I_{Kr}$  and  $I_{Ks}$  increased by 200%), the Nygren et al. [11] model can produce AP similar to the Courtemanche et al. model.

Simulations of AF were based on experimental data of two independent studies on human atrial myocytes, one reported by Bosch et al. [4] (AF-1) and the other by Workman et al. [5] (AF-2). In both studies, atrial myocytes were isolated from the right atrial appendages, but with different definitions of permanent AF: in the study of Bosch et al. [4], permanent AF was defined as a chronic AF at  $\geq 1$  month duration, while in the study of Workman et al. [5], it was defined as a chronic AF at  $\geq 6$  months duration. AF-induced changes in ion channels involve the same channels, but are quantitatively different between the two studies. In the AF-1 study, the statistically significant changes include an up-regulation of  $I_{K1}$  (by 235%), down-regulation of  $I_{CaL}$  (by 74%), down-regulation of  $I_{to}$  (by 85%), a shift of the activation curve of  $I_{to}$  (by 16 mV), and inactivation curve of  $I_{Na}$  (by 1.6

mV) in the depolarizing direction. The kinetics of the fast inactivation of  $I_{CaL}$  was slowed down by a 62% increase in the time constant. In the AF-2 study, the statistically significant changes include an up-regulation of  $I_{K1}$  (by 90%), down-regulation of  $I_{CaL}$  (by 64%), and down-regulation of  $I_{to}$  (by 65%). Details of the kinetics and conductance of some AF remodeled ion channels in the two models are listed in Table 1 and are compared to experimental data reported by Bosch et al. [4] and Workman et al. [5].

The modified models were used to simulate APs of human atrial myocytes, and were evoked by a series of supra-threshold stimuli (with an amplitude of  $-1.3$  nA and a duration of 6 ms for the Nygren et al. model; and  $-2$  nA and 2 ms for the Courtemanche et al. model) with a basic cycle length of 500 ms (2 Hz). The action potential duration at 90% repolarisation (APD<sub>90</sub>) of the 10th AP (by which time both models have approached a periodic state), resting potential (RP), and amplitude (AM) were computed from the standard and the AF remodeled models, and were compared with the experimental data reported by Bosch et al. [4] and Workman et al. [5] for atrial myocytes from patients in normal sinus rhythm (SR) and AF. Fig. 1 shows the simulated action potentials using the Nygren et al. model (left panels) and Courtemanche et al. model (right panels) with normal and AF remodelled parameters (AF-1: A and B; AF-2: C and D). With AF-1 remodelled parameters, simulated AF induces a 4 mV hyperpolarization of the resting potential (RP) and a 62% reduction in APD<sub>90</sub> for the Nygren et al. model; and a 4 mV hyperpolarisation of the RP and a 68% reduction in APD<sub>90</sub> for the Courtemanche et al. model. These changes in both models are quantitatively consistent with the experimental data observed by Bosch et al. [4] (2.6 mV hyperpolarisation of the RP and 60% reduction in the APD<sub>90</sub>.) With the AF-2 remodelled parameters, simulated AF induces a 4 mV hyperpolarization of the resting potential (RP) and a 47% reduction in APD<sub>90</sub> for the Nygren et al. model; and a 3 mV hyperpolarisation of the RP and a 49% reduction in APD<sub>90</sub> for the Courtemanche et al. model, which are quantitatively consistent with the experimental data reported by Workman et al. [5] (2 mV hyperpolarisation of the RP and 45% reduction in the APD<sub>90</sub>). Details of AF-induced changes in AP of the two models are listed and compared to the experimental data as shown in Table 2.

The relative importance of different remodeled ionic channels in the APD reduction was determined by two different methods: the removal and exclusive methods [12]. With the removal method, the AF-induced changes in only the channel of interest were omitted, while all other AF-induced changes were considered. With the exclusive method, the AF-induced changes in only the channel of interest were considered while all other AF-induced changes were omitted in the models. Numerically, these models were solved by the fourth Runge–Kutta method with a time step

Table 1

AF remodelling-related ion channel conductance, kinetics, and current density in the Nygren et al. [11] and Courtemanche et al. [10] models; and reported by Bosch et al. [4] and Workman et al. [5] obtained from human atrial myocytes under sinus rhythm (SR) and atrial fibrillation conditions

		Nygren et al. model	Courtemanche et al. model	Bosch et al. (experimental)			Workman et al. (experimental)		
				SR	AF	AF-induced change	SR	AF	AF-induced change
$C_m$	Membrane capacitance (pF)	50	100						
$I_{Ca,L}$	Channel conductance (nS/pF)	0.135	0.124						
	Voltage-dependent activation (mV)	$V_{0.5}=-9$ ; $k=5.8$	$V_{0.5}=-10$ ; $k=8$	$V_{0.5}=-0.1\pm 1.6$ ; $k=7.2\pm 1.4$	$V_{0.5}=-5.5\pm 4.0$ ; $k=7.8\pm 3.5$				
	Voltage-dependent inactivation (mV)	$V_{0.5}=-27.4$ ; $k=7.1$	$V_{0.5}=-28$ ; $k=6.9$	$V_{0.5}=-24.7\pm 0.3$ ; $k=6.6\pm 1.1$	$V_{0.5}=-25.5\pm 1$ ; $k=8.5\pm 1.13$				
	Peak current density (pA/pF)	-4.5	-3.58	$-6.97\pm 0.5$	$-1.88\pm 0.19$	73% ↓	$-6.04\pm 0.86$	$-2.17\pm 0.24$	64% ↓
	(+10 mV)	(+10 mV)	(+10 mV)	(+10 mV)	(+10 mV)		(+10 mV)	(+10 mV)	
$I_{to}$	Channel conductance (nS/pF)	0.15	0.17						
	Voltage-dependent activation (mV)	$V_{0.5}=1$ ; $k=11$	$V_{0.5}=1.5$ ; $k=10$	$V_{0.5}=18.7\pm 0.6$ ; $k=10.2\pm 0.5$	$V_{0.5}=34.6\pm 0.8$ ; $k=14.6\pm 0.7$	+16 mV			
	Voltage-dependent inactivation (mV)	$V_{0.5}=-40.5$ ; $k=1.5$	$V_{0.5}=-42.1$ ; $k=3$	$V_{0.5}=-40.3\pm 0.9$ ; $k=14.7\pm 0.8$	$V_{0.5}=-42.4\pm 1.4$ ; $k=17.5\pm 1.3$				
	Current density (pA/pF)	12.1	17.9	$7.84\pm 0.76$	$1.24\pm 0.28$	84% ↓	$9.23\pm 1.1$	$3.20\pm 0.5$	65% ↓
	(+50 mV)	(+50 mV)	(+50 mV)	(+50 mV)	(+50 mV)		(+50 mV)	(+50 mV)	
$I_{Na}$	Voltage-dependent activation (mV)	$V_{0.5}=-27.2$ ; $k=8.21$	$V_{0.5}=-42$ ; $k=8$	$V_{0.5}=-50.2\pm 0.2$ ; $k=5.3\pm 0.2$	$V_{0.5}=-48.6\pm 0.2$ ; $k=5.7\pm 0.2$	+1.6 mV			
$I_{K1}$	Channel conductance (nS/pF)	0.06	0.09						
	Current density (pA/pF)			$-9.83\pm 0.96$	$-19.91\pm 1.72$	102% ↑	$-3.5\pm 0.3$	$-6.7\pm 0.6$	90% ↑
				(-90 mV)	(-90 mV)		(-120 mV)	(-120 mV)	
				$0.85\pm 0.24$	$2.85\pm 0.63$	235% ↑			
				(-20 mV)	(-20 mV)				
							$-3.6\pm 0.2$		
							(-115 mV)		
		-1.15	-0.95	$-8.57\pm 1.5$					
		(-100 mV)	(-100 mV)	(-100 mV)					

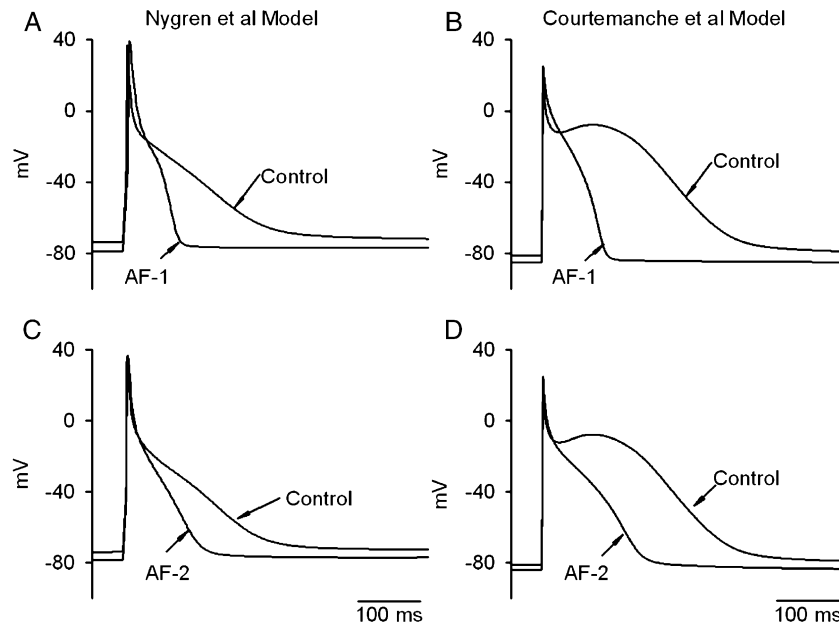


Fig. 1. Computed action potential of human atrial myocytes for normal and AF conditions using the Nygren et al. model and the Courtemanche et al. model. APs were produced by a series of supra-threshold stimuli (with an amplitude and duration of  $-1.3$  nA and  $6$  ms for the Nygren et al. model; and  $-2$  nA and  $2$  ms for the Courtemanche et al. model). AF-1: remodeled parameters were from the study of Bosch et al. [4]. AF-2: remodeled parameters were from the study of Workman et al. [5].

of  $10 \times 10^{-6}$  s for the Nygren et al. model, and  $5 \times 10^{-6}$  s for the Courtemanche et al. model. These time steps were small enough for stable numerical solutions. The program was coded in C<sup>2+</sup> and run on a Sunblade 2000 Solaris 9 Unix system.

### 3. Results

The individual roles and relative importance of AF remodelled ionic channels in APD reduction were investigated by using the removal and the exclusive methods. Fig. 2 shows simulations with the AF-1 remodelled parameters by using the removal method to the Nygren et al. (A–E) and the Courtemanche et al. (F) models. Panel A shows the effects of omitting the AF-induced changes in  $I_{to}$ , giving an APD<sub>90</sub> of  $79$  ms, a  $64\%$  reduction from the normal APD<sub>90</sub> of  $218$  ms. This is very close to the  $62\%$  reduction in APD<sub>90</sub> seen when all AF effects are considered. Results from the Courtemanche et al. model are similar (APD<sub>90</sub> is reduced by  $70\%$  when AF-induced changes in  $I_{to}$  are omitted, which is very close to  $68\%$  when all AF effects are considered), suggesting that AF-induced down-regulation of  $I_{to}$  contributes little to APD<sub>90</sub> reduction.

The effects of removing AF-induced remodelling of  $I_{CaL}$  channel current density and/or kinetics on the Nygren et al. model are shown in panels B, C, and D. Omitting remodelling of  $I_{CaL}$  channel kinetics, conductance, and both together, the AF remodelled parameters produced APD<sub>90</sub> reduction by  $62\%$ ,  $50\%$ , and  $51\%$ .

These values are close to the  $62\%$  reduction of APD<sub>90</sub> obtained when all AF actions are considered, suggesting that AF-induced down-regulation of  $I_{CaL}$  has a limited contribution to APD reduction. The results are similar with the Courtemanche et al. model: omitting AF remodelling of the  $I_{CaL}$  channel kinetics, conductance, and both together, there is  $68\%$ ,  $35\%$ , and  $43\%$  reduction in APD<sub>90</sub>, respectively.

In contrast to the above, omitting the large AF-induced changes in  $I_{K1}$  had a dramatic effect on APD in the Nygren et al. model (Panel E), resulting in *abolition* of action potential repolarisation. Without a large outward current  $I_{K1}$ , during the time window of AP repolarisation marked by the small box in the figure, the inward current balanced the outward current, resulting in a zero total current that failed to repolarise cell membrane potential further. A new equilibrium of membrane potential is reached before a full AP repolarisation is completed. Simulations using the Courtemanche et al. model showed that omitting the up-regulation of  $I_{K1}$  AF produced a reduction of  $35\%$  in APD<sub>90</sub>, much less than the  $68\%$  reduction of APD<sub>90</sub> produced when all AF actions were considered (panel F). These results highlight the importance of remodelling of  $I_{K1}$  in determining the overall effects of AF on the human action potential.

Omitting individual AF remodelling actions produced similar changes in AP configurations and APD<sub>90</sub> in both the Nygren et al. and the Courtemanche et al. models except for  $I_{K1}$ . Omitting up-regulation of  $I_{K1}$  in the Courtemanche et al. model did not abolish the AP repolarisation that is seen in the Nygren et al. model. In

Table 2  
Characteristics of action potentials and APD<sub>90</sub> under control and AF conditions computed from the Nygren et al. [11] model and Courtemanche et al. [4] (AF-1) and Workman et al. [5] (AF-2)

			Nygren et al. model				Courtemanche et al. model			
			AM (mV)	RP (mV)	APD <sub>90</sub> (ms)		AM (mV)	RP (mV)	APD <sub>90</sub> (ms)	
Control AF-1 (Bosch et al. [4] data)	AF	Change (Δ)	110	-74	218	Simulation Experiment	105	-81	308	
			115	-78	83		110	-85	98	
	AF	Change (Δ)	ΔAM=+5	ΔRP=-4	ΔAPD <sub>90</sub> =-136 (-62%)		ΔAM=+5	ΔRP=-4	ΔAPD <sub>90</sub> =-210 (-68%)	
			AM (SR)=116±3 AM (AF)=120±2 ΔAM=+4	RP (SR)=-76.3±2.2 RP (AF)=-78.9±2.9 ΔRP=-2.6	APD <sub>90</sub> (SR)=213±26 APD <sub>90</sub> (AF)=98±8 ΔAPD <sub>90</sub> =-115 (-60%)		AM (SR)=116±3 AM (AF)=120±2 ΔAM=+4	RP (SR)=-76.3±2.2 RP (AF)=-78.9±2.9 ΔRP=-2.6	APD <sub>90</sub> (SR)=213 APD <sub>90</sub> (AF)=98 ΔAPD <sub>90</sub> =-115 (-60%)	
AF-2 (Workman et al. [5] data)	AF	Change (Δ)	114	-78	115	Simulation Experiment	107	-84	156	
			ΔAM=+4	ΔRP=-4	ΔAPD <sub>90</sub> =-103 (-47%)		ΔAM=+2	ΔRP=-3	ΔAPD <sub>90</sub> =-152 (-49%)	
	AF	Change (Δ)	AM (SR)=126 AM (AF)=136 ΔAM=+10	RP (SR)=-76 RP (AF)=-78 ΔRP=-2	APD <sub>90</sub> (SR)=187 APD <sub>90</sub> (AF)=102 ΔAPD <sub>90</sub> =-85 (-45%)		AM (SR)=126 AM (AF)=136 ΔAM=+10	RP (SR)=-76 RP (AF)=-78 ΔRP=-2	APD <sub>90</sub> (SR)=187 APD <sub>90</sub> (AF)=102 ΔAPD <sub>90</sub> =-85 (-45%)	

both models, AP repolarisation is mainly contributed by  $K^+$  currents that include  $I_{to}$ ,  $I_{sus}$  ( $I_{Kur}$  in the Courtemanche et al. model),  $I_{Kr}$  ( $I_{Kf}$  in the Nygren et al. model),  $I_{Ks}$ , and  $I_{K1}$ . While both models have used similar current densities for  $I_{to}$  (the measured maximal current density during the time course of AP is about 10 pA/pF for the Courtemanche et al. model and 9 pA/pF for the Nygren et al. model),  $I_{sus}$  (4 pA/pF for the Courtemanche et al. model and 6 pA/pF for the Nygren et al. model), and  $I_{K1}$  (0.5 pA/pF for both models), the Courtemanche et al. model has significant greater current densities for  $I_{Kr}$  and  $I_{Ks}$ . The measured maximal current densities of  $I_{Kr}$  and  $I_{Ks}$  during the time course of AP are about 0.3 pA/pF and 0.11 pA/pF, respectively, for the Courtemanche et al. model, and are 0.030 pA/pF and 0.014 pA/pF, respectively, for the Nygren et al. model. The larger absolute and relative current densities of the delayed rectifier  $K^+$  currents,  $I_{Kr}$  and  $I_{Ks}$ , in the Courtemanche et al. model [11] are sufficient to overcome the inward current and allow full AP repolarisation.

Fig. 3 shows results obtained from applying the exclusive method to the Nygren et al. model. Panel B shows the action potential that results when  $I_{to}$  is the only current that is remodeled. There is an increase in APD<sub>90</sub> by 13% (i.e., down-regulation of  $I_{to}$  does not contribute to APD reduction, but tends to prolong APD). This is consistent with experimental observations using 4-AP on human atrial myocytes where blocking  $I_{to}$  produced APD prolongation [5]. The equivalent simulations using the Courtemanche et al. model showed a small overall APD<sub>90</sub> reduction (11%). These results suggest that  $I_{to}$  does not play a significant role in AF-induced APD reduction.

Panels C, D, and E show the AF induced changes on the  $I_{CaL}$  kinetics and channel conductance using the exclusion method. The resulting APD<sub>90</sub> reduction in these cases is markedly less than the 62% APD<sub>90</sub> reduction produced when all actions were considered. Simulations using the Courtemanche et al. model showed similar results. AF action on  $I_{CaL}$  channel kinetics, channel conductance, and both combined produced -4%, 28%, and 27% APD<sub>90</sub> reduction. Results from both models suggest that the AF-induced remodelling of  $I_{CaL}$  is not the primary factor producing APD<sub>90</sub> reduction.

Panel F shows the result when the AF-induced remodelling of  $I_{K1}$  alone was considered. AF-induced up-regulation of  $I_{K1}$  alone produced a 64% reduction in APD<sub>90</sub>, similar to the 62% reduction when AF-induced remodelling of all channels is considered. For the Courtemanche et al. model, AF-induced up-regulation of  $I_{K1}$  alone produced an APD<sub>90</sub> of 183 ms, a 40% reduction of APD<sub>90</sub>. For both models, AF-induced up-regulation of  $I_{K1}$  is the predominant mechanism in producing APD reduction.

Simulations using the AF-2 remodelled parameters were shown in Fig. 4. For the Nygren et al. model (Fig. 4A and B), omitting the AF action on  $I_{K1}$ , AF parameters produced



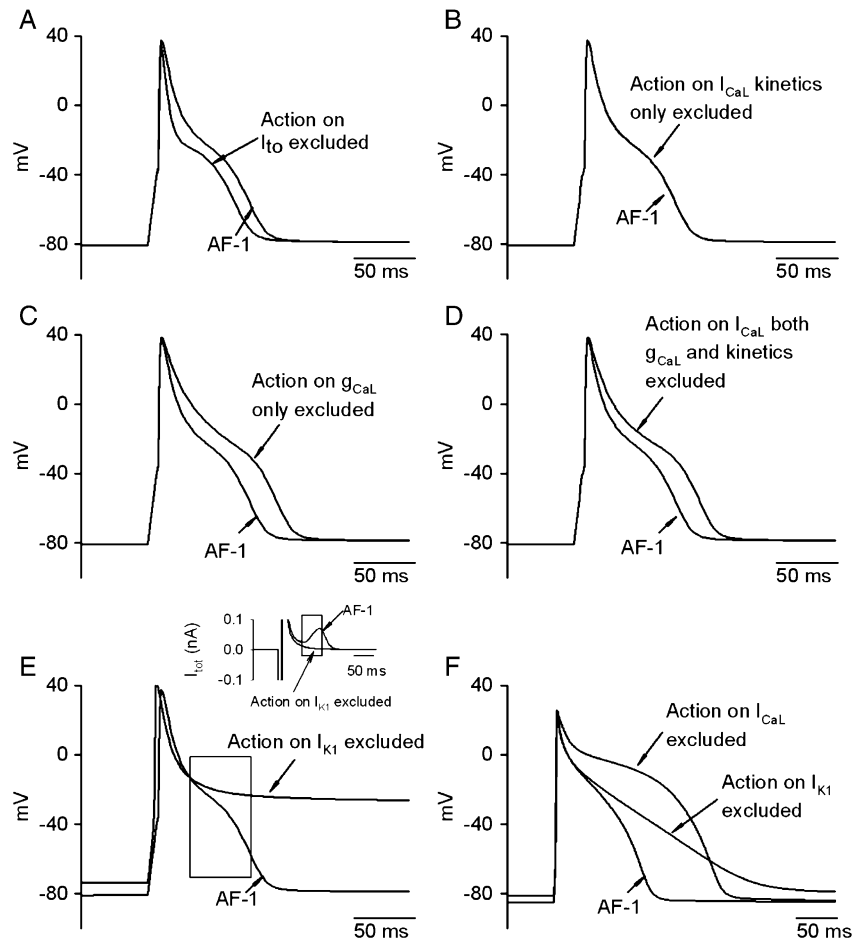


Fig. 2. The role of individual remodelled ionic channels in the AF-induced changes reported by Bosch et al. [4] in the electrical activity of the Nygren et al. (A–E) and Courtemanche et al. (F) models by the removal method. (A) AF remodelling of  $I_{to}$  was omitted. (B) AF remodelling of  $I_{CaL}$  kinetics was omitted. (C) AF remodelling of  $I_{CaL}$  channel conductance was omitted. (D) AF remodelling of  $I_{CaL}$  channel kinetics and conductance was omitted. (E) AF remodelling of  $I_{K1}$  was omitted. Insert: time course of total cell ion channel current during AP. During the time window marked by the box, a zero net total current failed to further repolarise cell membrane potential. (F) AF remodelling of  $I_{CaL}$  or  $I_{K1}$  was omitted in the Courtemanche et al. model.

a 15% reduction of  $APD_{90}$ , less than the 47% reduction of  $APD_{90}$  when all AF actions were considered. However, when the AF action on  $I_{CaL}$  is removed, there was a 36% reduction of  $APD_{90}$ , closer to the 47% reduction of  $APD_{90}$  when all AF actions were considered. When the AF action on  $I_{K1}$  alone was considered, there is a 40% reduction of  $APD_{90}$ , much greater than the 20% reduction of  $APD_{90}$  when the AF action on  $I_{CaL}$  alone was considered. Both simulations suggested that the up-regulation of  $I_{K1}$ , rather than the down-regulation of  $I_{CaL}$ , plays a primary role in  $APD_{90}$  reduction.

Results from the Courtemanche et al. model (Fig. 4C and D) showed similar findings. Omitting the AF action on  $I_{K1}$ , there was a 17%  $APD_{90}$  reduction, which is significantly less than the 49% reduction of  $APD_{90}$  when all AF actions were considered. When the AF action on  $I_{CaL}$  was removed, there was a 30% reduction of  $APD_{90}$ , closer to the 49%  $APD_{90}$  reduction when all AF actions were included. When the AF action on  $I_{K1}$  alone was considered, there is a 21%  $APD_{90}$  reduction, which is

greater than a 14%  $APD_{90}$  reduction when the AF action on  $I_{CaL}$  alone was considered.

During the time course of chronic AF, different degrees of AF remodelling that generate different changes to ion channel conductance and/or kinetics may occur. In the study of Bosch et al.,  $I_{K1}$  was increased by 235% (at  $-20$  mV) and  $I_{CaL}$  was decreased by 73%. However, in the study of Workman et al.,  $I_{K1}$  was increased by 90% and  $I_{CaL}$  was decreased by 64%. Although the changes of  $I_{CaL}$  were consistent in the two studies, the changes in  $I_{K1}$  differ widely. In order to evaluate the effects of possible degrees of AF remodelling on human atrial  $APD_{90}$  reduction, a series of simulations was performed with  $I_{K1}$  increased or  $I_{CaL}$  decreased to different levels, either alone or combined with other AF remodelling actions. The results were shown in Fig. 5.

Fig. 5A showed action potentials when  $I_{K1}$  alone was increased by 100%, 150%, and 200%. Such changes produced a reduction of  $APD_{90}$  by 42%, 51%, and 58%, respectively, for the Nygren et al. model. In Fig. 5B,  $I_{CaL}$

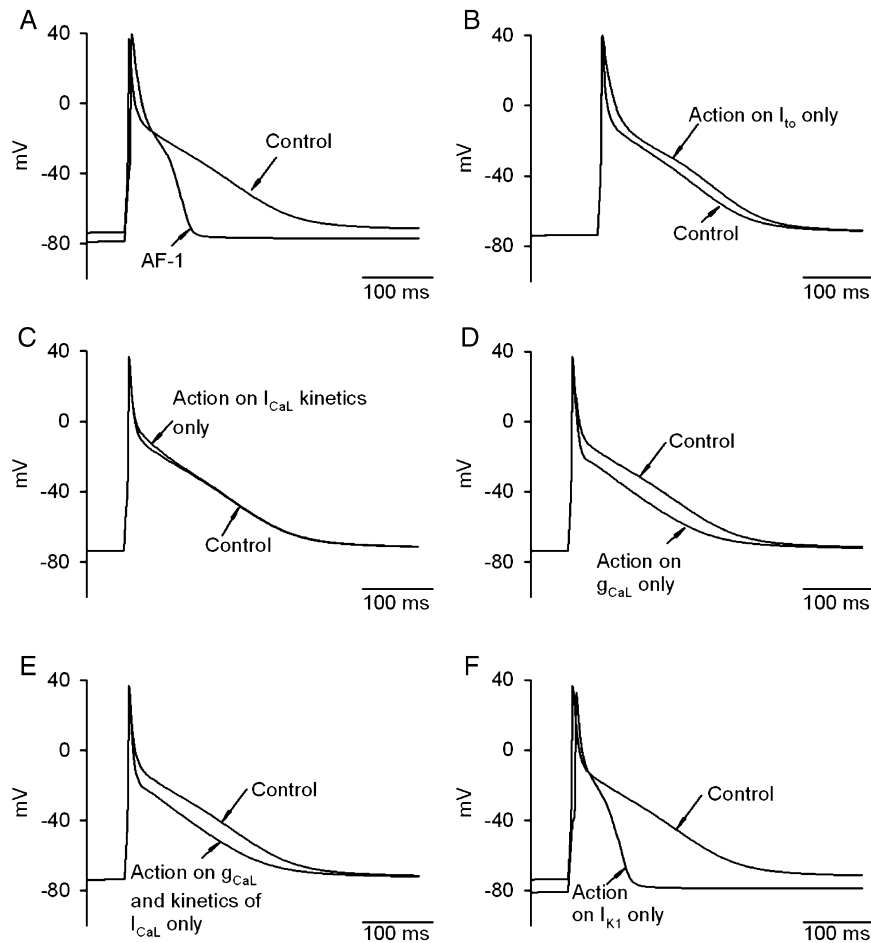


Fig. 3. The role of individual remodelled ionic channels in the AF-induced changes in the electrical activity of the Nygren et al. model by the exclusive method. (A) Action potential computed from the normal and AF remodelled models with all AF actions considered. (B) AF action on  $I_{to}$  only was considered. (C) AF action on  $I_{CaL}$  kinetics only was considered. (D) AF action on  $I_{CaL}$  channel conductance only was considered. (E) AF action on  $I_{CaL}$  channel kinetics and conductance only was considered. (F) AF action on  $I_{K1}$  only was considered.

alone was decreased by 25%, 50%, and 75%, which produced a reduction of  $APD_{90}$  by 13%, 20%, and 24%. Compared to the experimental data reported by Bosch et al. and Workman et al., a possible increase of  $I_{K1}$  to a modest level (by 100%) generated a 42%  $APD_{90}$  reduction that is closer to the 60%  $APD_{90}$  reduction when all AF actions were considered. However, a possible decrease of  $I_{CaL}$  to a maximal level (by 75%) only produced a 24%  $APD_{90}$  reduction.

In Fig. 5C,  $I_{K1}$  was increased in combination with other AF actions by 100%, 150%, and 200%. Such changes generated a reduction of  $APD_{90}$  by 29%, 44%, and 51%. In Fig. 5D, similar simulations were done when  $I_{CaL}$  was decreased by 25%, 50%, and 75% in combination with other AF actions. These changes produced a reduction of  $APD_{90}$  by 50%, 55%, and 58%, respectively. Increase of  $I_{K1}$  by 100% (comparable to the experimental data of Workman et al. [5]) to 200% (comparable to the experimental data of Bosch et al. [4]) altered  $APD_{90}$  reduction significantly. However, decrease of  $I_{CaL}$  by 25–75% level had little change to the  $APD_{90}$  reduction.

#### 4. Discussion

The main findings of this study are: 1) AF-induced APD reduction in human atrial myocytes can be sufficiently accounted for by the AF-induced changes in the ionic channels of  $I_{CaL}$ ,  $I_{to}$ , and  $I_{K1}$ , and 2) the remodeling of  $I_{K1}$  by AF appears to have the most influence on the AF-modified action potential of human atrial myocytes, with the remodeling of  $I_{CaL}$  having a significant but secondary role.

The ionic mechanisms underlying the AF-induced APD reduction of atrial myocytes have been examined most comprehensively in non-human species. Yue et al. [7] examined the development of ionic and cellular changes associated with a rapid atrial pacing model of AF in dogs for 1, 7, or 42 days. APD shortening was evident within 1 day of rapid pacing (27%) and was virtually complete by 7 days (47% at 42 days). This shortening was accompanied by a progressive decline in L-type Ca current and  $I_{to}$  amplitude, with no change in  $I_{K1}$  (−3 pA/pF at −90 mV),  $I_{Kr}$ ,  $I_{Ks}$ ,  $I_{CaT}$ , or  $I_{Cl,Ca}$ . At different states of pacing (i.e., at Control, 1, 7, and 42 days of pacing), the measured  $I_{Ca}$  current density (at

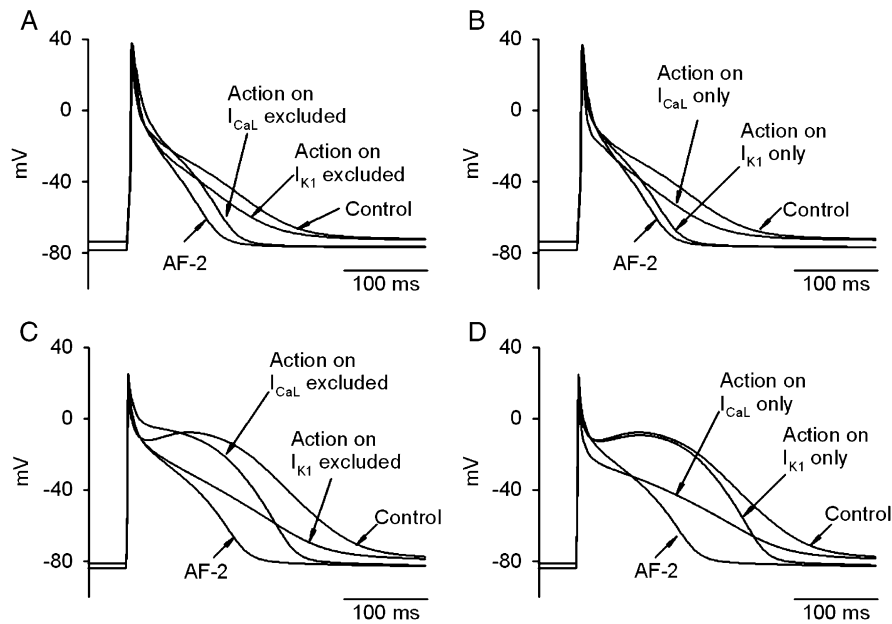


Fig. 4. The role of individual remodelled ionic channels in the AF-induced changes reported by Workman et al. [5] on the electrical activity of the Nygren et al. (A and B) and Courtemanche et al. (C and D) models by the removal and the exclusive methods. (A) AF remodelling of  $I_{CaL}$  or  $I_{K1}$  was omitted in the Nygren et al. model. (B) AF remodelling of  $I_{CaL}$  or  $I_{K1}$  only was considered in the Nygren et al. model (C) AF remodelling of  $I_{CaL}$  or  $I_{K1}$  was omitted in the Courtemanche et al. model. (D) AF remodelling of  $I_{CaL}$  or  $I_{K1}$  alone was considered in the Courtemanche et al. model.

+10 mV) changed from  $-12.2 \pm 0.8$  pA/pF to  $-8.4 \pm 0.5$  pA/pF,  $-5.9 \pm 0.4$  pA/pF, and  $-3.8 \pm 0.2$  pA/pF, respectively; the measured  $I_{to}$  current density (at +50 mV) changed from 11.7 pA/pF to 8.7 pA/pF, 5.9 pA/pF, and 4.6 pA/pF, respectively. Similar reductions in APD to those seen in chronically paced dogs were produced by exposure to

nifedipine in normal cells, suggesting that depression of  $I_{Ca}$  was responsible for much of the APD shortening in paced dogs. Blockade of  $I_{to}$  caused little further change in APD to that seen with blockade of  $I_{Ca}$ . Other biophysical properties of the currents, including voltage and time dependence, were unaltered, suggesting that there is a decrease in the

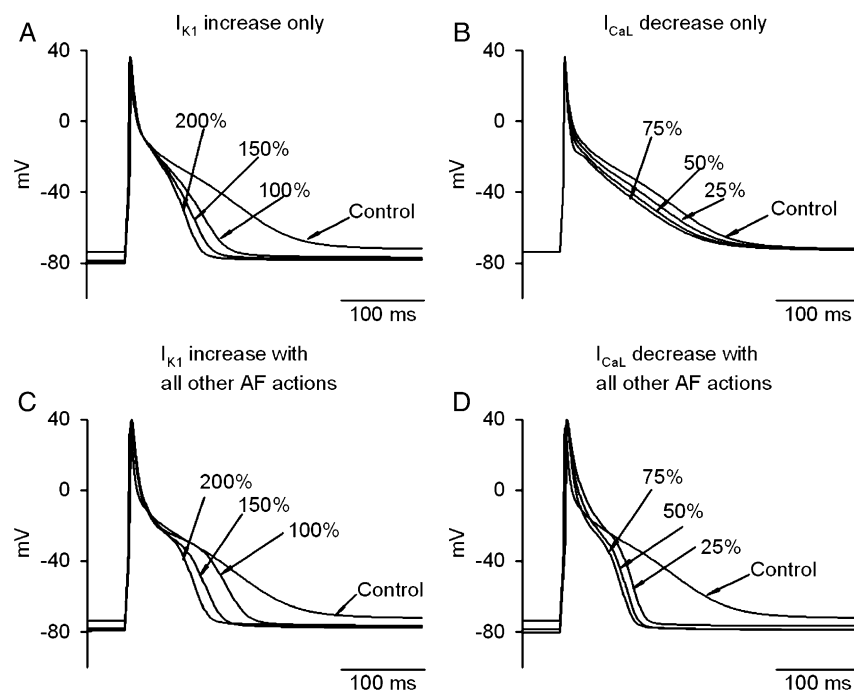


Fig. 5. Effects of various changes of  $I_{K1}$  and  $I_{CaL}$  on action potentials of the Nygren et al. model. (A) Various increases of  $I_{K1}$  alone. (B) Various decrease of  $I_{CaL}$  alone. (C) Various increase of  $I_{K1}$  in combination of all other AF actions reported by Bosch et al. [4]. (D) Various decrease of  $I_{CaL}$  in combination of all other AF actions reported by Bosch et al. [4].



number and/or conductance of  $I_{Ca}$  channels without a change in their fundamental nature. Primarily as a consequence of these studies, down-regulation of Ca channels has been considered to be the main molecular mechanism of AF-induced reduction of APD.

In humans, however, AF-induced changes are more complex and include up-regulation of  $I_{K1}$  current density, down-regulation of  $I_{CaL}$  and  $I_{to}$  current densities, and changes in the kinetics of  $I_{to}$ ,  $I_{CaL}$ , and  $I_{Na}$  channels [3–5]. Our current results suggest that up-regulation of  $I_{K1}$  current density in the order of magnitude identified by Bosch et al. [4] or Workman et al. [5] has the predominant effect in terms of APD reduction, rather than down-regulation of  $I_{Ca}$ . These findings are consistent with the experimental observation of Workman et al. [5] on human atrium, in which the whole cell patch clamp technique was used to study the electrophysiology of isolated myocytes of patients undergoing cardiac surgery. In this study, nifedipine (10  $\mu$ mol/L) virtually abolished  $I_{CaL}$  but produced only a small reduction in APD<sub>75</sub> and APD<sub>90</sub> (by 29% and 17%, respectively), with no accompanying effect on the effective refractory period. The authors concluded that an exclusive reduction in  $I_{CaL}$  would be insufficient to explain AF-induced remodeling of action potentials and the effective refractory period in human atrial myocytes.

There is evidence from other sources that up-regulation of  $I_{K1}$  may be relevant to increased stability of AF. Atrial fibrillation, like ventricular fibrillation, is thought to be based on multiple electrical wavelets wandering throughout the tissue with constantly changing direction. Although the meandering of these wavelets has been considered to be a random or near-random process, recent studies have demonstrated spatiotemporal periodicities in electrical activation during both forms of fibrillation [13]. This has led to the rekindling of the hypothesis that fibrillation is maintained by wavefronts emanating at high frequency from a relatively stable source, possibly in the form of a rotor. Mansour et al. [14] have suggested that the gradient of excitation frequencies between the right and left chambers in both atrial and ventricular fibrillation is an expression of such sources located in the left atrium or ventricle, respectively. Using patch clamp techniques in guinea pig preparations, they have shown an association between the amplitude of the outward component of  $I_{K1}$  and this gradient between the left and right ventricles during VF [15]. They hypothesize that, in addition to controlling APD, a large  $I_{K1}$  stabilizes such a rotor during fibrillation and is of considerable importance in the maintenance of the arrhythmia. More recently, this group has used optical mapping techniques in the presence of  $Ba^{2+}$  to selectively block  $I_{K1}$  in ventricular myocytes and have shown that this results in a reduction in frequency gradient during VF and leads to termination of VF in a dose-dependent manner [16].

AF-induced remodeling also includes anatomical structure [17] and intercellular gap junction coupling [18–21], which are believed to play important roles in AF self-

perpetuation. The relative roles of conductance, and anatomical and gap junction remodeling in AF maintenance are incompletely understood. For anatomical re-entry where there is a clear excitable gap that may be lengthened in chronic AF by gap junctional remodeling, the reduced APD will be less important. However, it is certain that the APD reduction produced by conductance remodeling shortens the excitation wavelength, and so will facilitate the initiation and persistence of re-entry.

## 5. Limitations of the study

In simulations, we have not incorporated the AF-induced changes in the intracellular  $Ca^{2+}$  handling [22,23] into the models as limited experimental data are available. Other factors associated with AF-induced changes in the intracellular  $Ca^{2+}$  handling, such as ion transport via  $Na^+-Ca^{2+}$  exchanger [24] and  $Na^+-K^+$  pump [25] may also play certain role in APD shortening, which have not been considered here as limited experimental data available. Nevertheless, without considering AF-induced changes in intracellular  $Ca^{2+}$  transient, AF-induced changes in various ionic channel kinetics and conductance can produce APD reduction that is quantitatively comparable to the experimental data. The findings of this study are, of course, dependent upon the experimental details of two independent studies [4,5], although up-regulation of  $I_{K1}$  is a consistent finding amongst studies of AF-induced ionic changes in humans [3,5,26].

## 6. Clinical implications

Differences in the mechanism of remodeling between canine and human atrial tissue clearly have considerable significance in terms of the future development of specific “anti-remodeling” therapy for use in patients with clinical forms of AF. Some groups have suggested the use of calcium channel antagonists to suppress remodeling in patients with AF, based primarily on experiments in dogs or goats in which use of verapamil has attenuated AF-induced reductions in atrial refractory period. There is also some observational human data supportive of this suggestion. Data in humans are conflicting, however, with the majority of studies indicating an increase in AF stability associated with the use of verapamil. The current study raises the possibility that AF-induced APD reduction maybe mediated primarily by an up-regulation of  $I_{K1}$  and this offers a potential further target for the development of anti-remodeling treatment.

## Acknowledgement

This work was supported by a grant from the EPSRC (GR/S03027/01) and the BHF (PG/03/140/16236) UK.

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