Cellular Modelling of Electrical Remodelling in Two Different Models of Human Atrial Myocytes

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Abstract

Changes in action potentials of atrial myocytes and various ionic channels induced by chronic atrial fibrillation (AF) have been described in the human. The mechanisms underlying the AF-induced action potential duration (APD) shortening have not been clearly identified. In this study we modify two different computational models of electrical activity of human atrial myocytes by incorporating chronic AF induced changes in several of the ionic channels systems found in myocytes. We examine the ionic mechanisms underlying the AF induced APD reduction and the relative roles of different remodeled ionic channels in producing the APD reduction. In both models we have found that AF induced changes in the ionic channel conductances and kinetics are able to reproduce the APD reduction seen experimentally. AF-induced down regulation of L-type Ca current is insufficient to account for the observed APD reduction, but up regulation of I_{K1} has a much greater influence.

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 the human [3-5]. Among these changes, action potential duration (APD) shortening is predominant and believed to underlie the mechanisms of "AF begetting AF" [1]. APD shortening is expected to allow the initiation and favour the maintenance of multiple reentrant wavelets in a limited mass of atrial tissue [1, 6].

The mechanisms underlying the AF-induced APD reduction of atrial myocytes have not been clearly identified. It may be due to AF induced changes in the expression of various ionic channels. In a canine model, AF induces down regulation of the current densities of I_{Ca} and I_{to} [7]. AF induced APD reduction can be reproduced by application of nifedipine to block I_{CaL}. Thus down-regulation of I_{CaL} has been thought to be the main mechanism producing APD shortening with AF [7]. In the human atrium, AF induces up-regulation of I_{K1}, down-regulation of I_{CaL} and I_{to} current densities and changes in the kinetics of I_{to}, I_{CaL} and I_{Na} [3-5]. The relative role of these changes in channel regulation on APD shortening is unclear. Unlike the canine model, the role of down regulation of I_{CaL} in producing APD reduction in human atrium is questionable as abolishing I_{CaL} by 10μM nifedipine generates only a small APD reduction in human atrial myocytes [5]. In order to investigate the ionic mechanisms underlying the AF induced APD reduction in human atrium and the relative roles of individual remodelled ionic channels in producing APD reduction we have modified two computational models of electrical activity of human atrial myocytes [8-9] by incorporating chronic AF induced changes in various ionic channel conductances and kinetics into the models. With the modified models we apply the methods of Zhang *et al*. [10] to examine quantitatively the ionic mechanisms underlying the APD reduction and the relative role of the different types of ionic channel in producing APD reduction for human atrial cells in AF.

2. Results

Based on a similar set of experimental data two independent models of electrical activity of human atrial myocytes have been developed by Nygren *et al*. [8] and Courtemanche *et al*. [9]. Both models were validated and can reproduce action potentials of human atrial myocytes in normal physiological and pathological conditions. We have modified the two cellular models to incorporate the experimental data of AF induced changes in ionic channel conductance and kinetics of human atrial myocytes reported experimentally by Bosch *et al*. [4] and Workman *et al*. [5]. These AF induced changes include an up regulation of I_{K1} (the channel conductance was increased by 250%), down regulation of I_{CaL} (the channel conductance was decreased by 74%), down regulation of I_{to} (the channel conductance was decreased by 85%), the shift of 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 by a 62% increase in the time constant. With these changes, both models can reproduce the action potential of human atrial myocytes with chronic AF. The model-generated action potentials under normal (control) and AF conditions were shown in Figure 1.

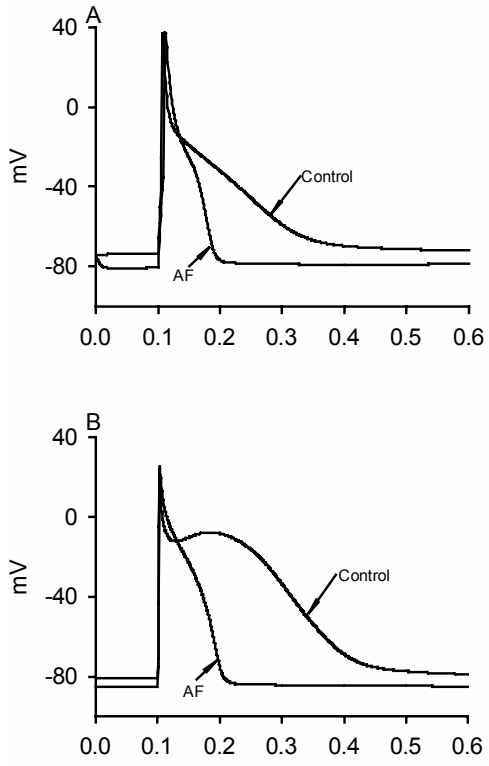

Figure 1. Computed action potential of human atrial myocytes for normal (control) and chronic atrial fibrillation (AF) conditions, produced by a supra-threshold stimulus with 0.6 nA amplitude and 4 ms duration. A) Action potential computed from the Nygren et al. model [8]. B) Action potential computed from the Courtemanche et al. [9] model.

The simulated action potentials with normal (control) and AF conditions show differences. With the Nygren *et al*. model the normal action potential has a resting potential (RP) of -74 mV and an APD_{90} of 300 ms. The AF remodelled action potential has a RP of -78 mV and an APD_{90} of 105 ms. Simulated AF remodelled parameters induces a 4 mV hyperpolarisation of the RP and a 65% reduction in APD_{90}. With the Courtemanche *et al*. model the results are similar: AF induced a 4 mV hyperpolarisation of the RP and a 68% reduction in APD_{90}. These changes in action potential computed from both models are quantitatively consistent with the experimental data observed by Bosch *et al*. [4] who have shown that the action potentials recorded from isolated atrial cells from patients with normal sinus rhythm are different to the action potentials recorded from isolated atrial cells from patients with chronic AF. With AF there was about 3 mV hyperpolarisation of the RP and about 58% reduction in the APD_{90} [4].

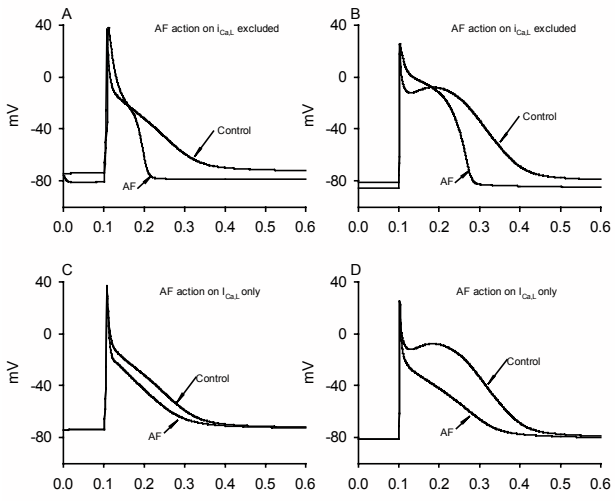

Figure 2. The role of AF induced remodeling of I_{CaL} in producing APD reduction in computer models of electrical activity of human atrial myocytes. Action potential computed from the standard models was superimposed with action potential computed with AF remodelled models. A & B) Action potential computed from the AF remodelled models when AF action on I_{CaL} was omitted by using the Nygren *et al.* (A) and the Courtemanche *et al*. (B) models. C & D) Action potential computed from the AF remodelled models with AF action on I_{CaL} only was considered by using the Nygren *et al*. model (C) and the Courtemanche *et al*. model (D).

The relative importance of different remodelled ionic channels in the APD reduction was determined by two different methods: the removal and exclusive methods [10]. With the removal method, the AF-induced changes in the channel of interest were omitted while all other AF-induced changes were considered in the models. With the exclusive method, the AF-induced changes in the channel of interest only were considered while all other AF-induced changes were omitted in the models.

Figure 2 shows the relative role of AF induced changes of I_{CaL} in producing APD reduction using the removal and the exclusive methods. With the Nygren *et al*. model, omitting the AF induced remodelling of I_{CaL} by the removal method, the AF remodelled parameters produced APD_{90} reduction by 61% (Figure 2A). This value is close to the 65% reduction of APD_{90} obtained when all AF actions are considered. For the Courtemanche *et al*. model without AF remodelling of the I_{CaL} (Figure 2B) there is a 43% reduction in APD_{90}.

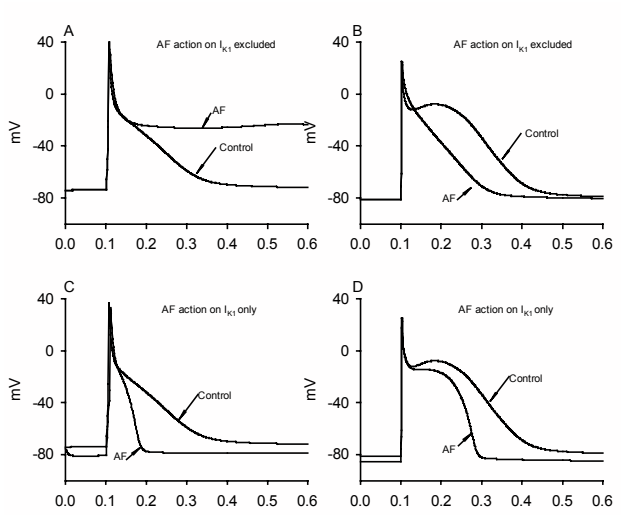

Figure 3. The role of AF induced remodeling of I_{K1} in producing APD reduction in computer models of electrical activity of human atrial myocytes. Action potential computed from the standard model was superimposed with action potential computed with AF condition. A) & B) Action potential computed from the remodelled models when AF action on I_{K1} was omitted by using the Nygren *et al*. model (A) and the Courtemanche *et al*. model (B). C) & D) Action potential computed from the AF remodelled models when AF action on I_{K1} only was considered by using the Nygren *et al*. model (C) and the Courtemanche *et al*. model (D).

Though AF induced down regulation of I_{CaL} contributed to APD reduction in the Courtemanche *et al*. model, the contribution was limited and cannot sufficiently account for the APD reduction produced when all AF induced changes were considered. In both models omitting AF remodelling on I_{CaL} does not affect APD reduction significantly. Down regulation in I_{CaL} is not the primary factor generating APD_{90} reduction in AF.

Consistent results have been obtained by using the exclusive method. With the Nygren *et al*. model the AF induced changes on I_{CaL} alone (Figure 2C) generated a 12% APD_{90} reduction. The resulted APD_{90} reduction is less than the 65% APD_{90} reduction produced when all actions were considered. Simulations using the Courtemanche *et al*. model showed similar results (Figure 2D). AF action on I_{CaL} produced a 27% APD_{90} reduction. This is much less than the 68% reduction when all AF actions were considered. In both models quantitatively the AF induced remodelling of I_{CaL} is not the primary factor producing APD_{90} reduction.

The role of AF induced up regulation of I_{K1} in producing APD reduction is illustrated in Figure 3. For the Nygren *et al*. model when AF induced change of I_{K1} is omitted from the AF remodelled parameters (Figure 3A), repolarisation of the action potential is abolished. Simulations using the Courtemanche *et al*. model showed that without the up regulation of I_{K1} AF produced a reduction of 35% in APD_{90}, which is significant less than the 68% reduction of APD_{90} produced when all AF actions were considered (Figure 3B). In both models up regulation of I_{K1} plays an important factor in producing APD_{90} reduction seen in AF.

For the Nygren *et al*. model AF induced up regulation of I_{K1} alone produced a 68% reduction in APD_{90}, similar to the 65% reduction when all AF induced remodelling were considered (Figure 3C). For the Courtemanche *et al.* model AF induced up regulation of I_{K1} alone produced a 40% reduction of APD_{90} that is larger than the 27% reduction of APD when AF induced remodeling of I_{CaL} alone was considered (Figure 3D). For both models AF induced up regulation of I_{K1} is the predominant mechanism in producing APD reduction.

The role of AF induced changes of I_{to} in producing APD reduction was also investigated. When AF induced remodelling of I_{to} was omitted, AF remodeled parameters generate is a 68% reduction in APD_{90} for the Nygren *et al*. model and a 70% reduction in APD_{90} for the Courtemanche *et al*. model. Both values are close to the 65% and 68% of APD_{90} reduction when all remodelled effects are considered for the Nygren *et al*. and Courtemenche *et al*. models respectively.

When AF induced remodelling of I_{to} alone was considered, with the Nygren *et al*. model, there is an increase in APD_{90} by 13%. With this model down regulation of I_{to} does not contribute to APD reduction, but on the contrary 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]. With the Courtemanche *et al*. model remodelling of I_{to} alone produced prolongation of the action potential at phase 1 and 2, as in the Nygren *et al*. model and experimental data of Workman et al. [5], but an overall APD_{90} reduction (11%). So AF remodelling of I_{to} does not contribute to APD reduction.

3. Conclusions

Two independent models of action potential of human atrial myocytes [8-9] have been modified to incorporate the experimental data of chronic AF induced changes on various ionic channel kinetics and conductances in human atrial cells [3-5]. Using the models we have investigated the ionic mechanisms underlying the AF induced APD reduction in human atrium and the relative importance of individual remodelled ionic channels in

producing APD reduction. We have shown that AF induced APD reduction in the electrical activity of 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}. This verifies the hypothesis that AF induced changes of the electrical activity of human atrial myocytes are *via* AF induced specific changes in the maximal conductances and kinetics of some of the membrane ionic channels. The relative importance of individual remodelled ionic channels has been investigated by two different methods - the removal and exclusive methods. Both methods gave consistent results and suggest that AF actions on the sarcolemmal I_{CaL} channels cannot produce an APD reduction comparable to that when all AF induced remodeling actions were considered. AF induced changes on I_{CaL} have been proposed to be the primary factor for AF induced APD reduction. This conclusion was based on the experimental data on canine atrial myocytes [7]. However, in human atrium both models have shown that AF remodelling of I_{CaL} contributed only partially to the APD reduction produced by AF.

The role of AF remodeling of I_{K1} is of interesting. With the removal method, removing AF remodelling of I_{K1} the repolarisation was abolished in the Nygren *et al*. model. With the exclusive method, AF remodelling of $I_{K,1}$ alone can produce APD reduction comparable to that when all AF remodelling was considered. In the Courtemanche *et al*. model, though removing AF remodelling of I_{K1} did not abolish repolarisation, it did produce the largest change in APD reduction; and AF remodelling on I_{K1} alone also produced the largest APD_{90} reduction we observed. Both models suggested that up regulation of I_{K1} by AF plays an important role in APD reduction.

Acknowledgements

This work was supported by a grant from the EPSRC (GR/S03027/01) UK.

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