Computational Study of the Relative Contribution of Channel and Gap Junction Remodelling on Human Atrial Conduction during Fibrillation

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Abstract

Chronic atrial fibrillation (AF) induces remodelling of both channel conductance and intercellular coupling in the human atrium. Effects of these changes and their relative contributions to atrial impulse conduction during fibrillation are unknown. In this study we constructed a virtual human atrial strand by incorporating the Nygren et al. model of human atrial action potential into a 1-dimensional reaction diffusion partial differential equation. Experimental data on AF-induced changes of human atrial ionic channel conductances and kinetics and gap junction coupling were incorporated into a model to investigate their contributions and relative importance on conduction velocity (CV) at different rates. At low rates (stimulus interval SI > 270 ms), AF-induced channel or gap junction remodelling reduced CV significantly. At high rates (SI<270 ms), channel remodelling increased CV while gap junction remodelling reduced the CV. When combined, channel and gap junction remodelling reduced CV additively. Spatial heterogeneities in gap junction coupling can produce intermittant conduction block.

1. Introduction

Chronic atrial fibrillation (AF) is the most common tachyarrhythmia that causes high morbidity and mortality [1]. Typically AF is characterised by high rate (300-500/min) activity that represents multiple re-entrant propagation in atria [2,3]. How the propagation of multiple re-entrant wavelets is maintained within a limited atrial mass is poorly understood.

The persistence of AF increases progressively with time [4.5]. This phenomenon is called AF self-perpetuation ("AF begets AF"), which was initially demonstrated in a chronically instrumented conscious goat model[4], and then confirmed in different animal models[5] and humans [6-8] by a number of different groups. In these studies increase of AF persistence is always associated with progressive changes (remodelling) in atrial properties that include anatomical structure [9], ionic channel kinetics [3-8] and intercellular gap junction coupling [10-14]. Amongst the most prominent change is a decrease in refractoriness produced by significant action potential duration (APD) shortening [3-8]. In the human a more hyperpolarized resting potential (RP) and decreased maximal upstroke velocity has been observed [6-7]. These electrical changes may be accounted by AF-induced remodelling of various sarcolemmal ion channels (kinetics and conductance). In humans, AF induces up regulation of I_{K1} channel density, down regulation of I_{CaL} and I_{to} channel densities and changes in the kinetics of I_{to}, I_{CaL} and I_{Na} channels [6-8].

Another important change is in the density and distribution pattern of the expression of connexins, the proteins that constitute the gap junction connections between myocytes [10-14]. In the goat model AF produces a heterogeneous decrease in the expression of connexin40 (Cx40) [10-12]. In humans, although no consistent pattern has emerged as yet, a change in the distribution of Cx40 and Cx43 have been observed [11,13].

AF-induced channel and gap junctional remodelling are believed to be the mechanisms underlying AF self-perpetuation, as they favor conduction of high rate activity. However, it is unclear how channel and gap junction remodelling affect atrial conduction during fibrillation. We assess their individual roles and relative importance by computer modelling.

2. Methods

Model of human atrial strand. A 1D model of a virtual human atrial strand with length 96 mm was constructed by incorporating the Nygren *et al*. model of human atrial action potential [15] into a nonlinear reaction diffusive partial differential equation (PDE) which takes the form:

$$\frac{dV(x,t)}{dt} = -\frac{1}{C_m}\sum_j i_j(x,V,t) + \nabla(D(x)\nabla V(x,t)) \quad (1)$$

V is the membrane potential, i_j the j-th gated membrane ionic channel current, C_m the cell membrane capacitance. x is the length along the atrial strand. D is the diffusion coefficient that simulates the intracellular,

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extracellular and membrane resistance and gap junctional coupling. D is a scalar for tissue with homogeneous, or a spatial function for tissue with heterogeneous gap junction coupling. D was set to 0.3125 cm^2s^{-1} across the control strand that gave a solitary plane wave conduction velocity 32 cm s^{-1} [16].

Simulation of AF. Experimental data of AF-induced channel changes in atrial ionic channel conductance and kinetics reported by Bosch *et al*. [7] in human have been incorporated into the Nygren *et al.* model of atrial action potential to simulate AF. 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%), 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. Gap junction remodelling was by decreasing D either uniformly for homogeneous remodelling or randomly for heterogeneous remodelling. In simulations D was reduced by 40% as suggested by previous study [14] or as specified in the text.

Stimulus protocols and measurement of CV. Excitation waves on the virtual atrial strand were triggered by standard S1-S2 protocol (with amplitude of -0.6 nA and a duration 8 ms) delivered at one end of the strand. CV at different stimulus intervals (SI) was computed as the ratio between the distance of two recording sites R1 and R2 and the time required for the excitation wave evoked by S2 to travel between them. R1 and R2 are 32.0 and 38.4 mm away from the stimulation site respectively.

Individual roles and relative importance of channel and gap junction remodelling on CV at different SIs were evaluated by incorporating the two individually or combined into the model. Conduction failure was quantified by the minimal or critical value of D (D_{min}) which supports stable wave conduction in the strand.

Measurement of atrial cell excitability. Atrial cell excitability is measured by its excitation threshold. A standard S1-S2 protocol was used to evoke action potential. S1 was supra-threshold with amplitude of -0.6 nA and duration 8 ms. S2 had variable amplitude but fixed duration (8ms). Excitation threshold was computed as the minimal amplitude of S2 which could evoke full action potential. In simulations, excitation thresholds with different rates (SIs) were computed for atrial cell model with normal and AF parameters.

Numerical implementation. Numerically the 1D PDE model was solved by the explicit Euler method with a three-node approximation of Laplacian operator. In numerical simulations a space step of 0.32 mm and a time step of 0.01 ms were used, which are sufficient small for stable numerical solutions. The program was coded in C^{++} and run on a Sunblade 2000 Solaris 5.8 Unix system.

3. Results

Figure 1A shows the simulated action potentials with normal and AF conditions. Simulated AF induces a 4 mV hyperpolarization of the resting potential and a 65% reduction in action potential duration (90% repolarisation). These changes are quantitatively consistent with the experimental data observed by Bosch *et al*. (3 mV hyperpolarisation of the resting potential and about 58% reduction in the action potential duration).

AF-induced channel remodelling decreases atrial excitability. Figure 1B shows the computed excitation threshold for atrial cell with normal and AF conditions at various stimulus intervals. It is apparently that AF remodelled cell has larger excitation threshold than normal cells. With SI=250 ms, the computed excitation threshold for the normal cell is 0.20 nA, and for the AF remodelled cell is 0.38 nA. Compared to the normal cell, AF-induced electrical remodelling reduced atrial excitability by 90%.

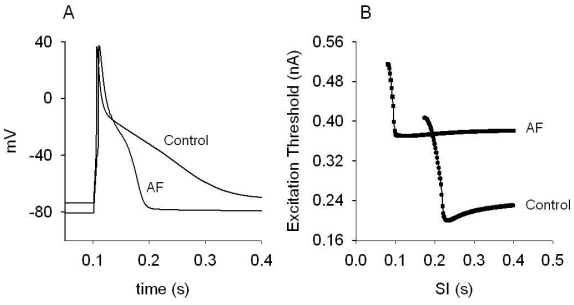

Figure 1. A) Simulated APs at normal and AF conditions evoked by a solitary super-threshold stimulus (with a duration 8 ms and amplitude of -0.6 nA). B) Computed atrial cell excitation threshold for second action potential for model with normal and AF parameters.

Atrial tissue's ability to propagate excitation waves was also decreased by AF-induced channel remodelling, illustrated by the decreased CV as shown in Figure 2. Without any change in gap junction coupling (i.e., 0% D deduction shown in figure) the computed CV is 0.32 m/s for normal atrial strand and 0.27 m/s for the AF remodelled strand. AF-induced channel remodelling alone decreased CV by 15.6%.

CVs computed from normal and AF channel remodelled strands with different levels of D reduction were also shown in Figure 2. In both models CV decreased with D monotonically. With 40% reduction in D, CV was reduced by 28% in normal tissue and 43.7% for the channel remodelled tissue compared to that in control condition. Further decreasing D resulted in conduction failure. In order to quantify atrial tissue's

ability to support conduction in normal and AF conditions D_{min} was estimated for normal and AF remodelled tissues. In normal tissue, D_{min} was up to 95% reduction of the standard D; while in the channel remodelled tissue D_{min} was up to 85% reduction of the standard D. This suggests that AF channel remodelled tissue requires larger cell-to-cell coupling to support conduction because of the reduction in excitability, as shown in Figure 1B.

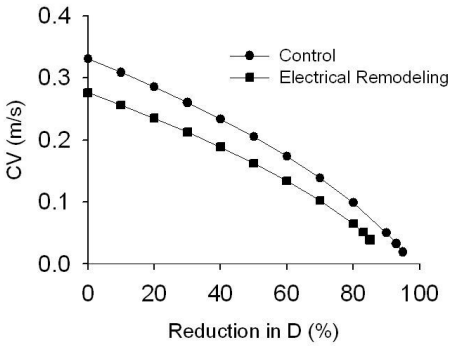

Figure 2. Effects of AF-induced channel remodelling on atrial conduction at various levels of D deduction.

Effects of channel and gap junction remodelling on atrial conduction velocity are rate dependent as shown in Figure 3, in which CV at various SIs was represented for normal, channel conductance remodelled, gap junction remodelled and combined remodelled tissues. Compared with normal tissue, AF-induced channel or gap junction remodelling reduced CV at low stimulus rates (SI>270 ms). At SI =400 ms, channel and gap junction remodelling produced 11% and 29% deduction in CV respectively. However, at high rates (SI<270 ms), channel remodelling increased CV while gap junctional remodelling reduced CV. At SI=250 ms, channel remodelling increased CV by 5.2% while gap junction remodelling decreased CV by 27%. Channel remodelling enabled atrial tissue to conduct high rate excitation waves that cannot be conducted in normal or gap junction remodelled tissues. With SI in the range of 110 ms < SI < 225 ms, close to the rate of atrial electrical activity during fibrillation, the excitation wave can only be conducted in the channel remodelled tissue. When combined, channel and gap junction remodelling, though they reduce CV additively, they enabled atrial tissue to conduct high rate activity. This demonstrated that AF-induced channel remodelling plays an important role in the propagation of activity during AF.

Effects of heterogeneous gap junction remodelling on atrial conduction was also investigated. Figure 4 represents propagation of action potentials along channel remodelled strands with two different cases. In case A gap junction remodelling was homogeneous (Figure 4A),

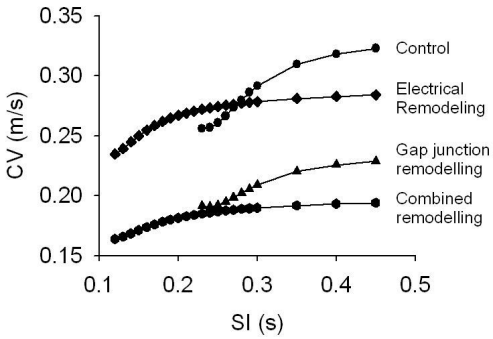

Figure 3. Rate dependent effects of AF-induced electrical and gap junction remodelling on atrial conduction and relative importance.

in which D was reduced uniformly by 80% along the strand. In this case a stable conduction was established. In case B gap junction remodelling was heterogeneous (Figure 4B), in which D was reduced by 64% to 80% randomly with space. In this case though the effective D was overall larger than that in case A (can be seen by a faster conduction velocity in B), but impulse conduction was unstable because of erratic and intermittent conduction block.

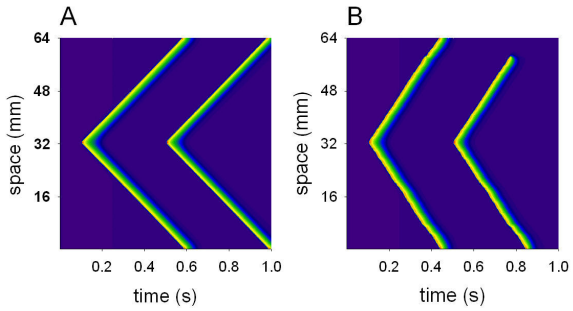

Figure 4. Space-time plot of atrial action potentials on AF remodelled strands in response to a series of supra-threshold stimuli with duration of 8 ms and amplitude of -0.6 nA applied to the middle of the strand. The evoked action potential spread as excitation waves bi-directionally. (A) Stable conduction in tissue with homogeneous gap junction remodelling. (B) Unstable conduction in tissue with heterogeneous gap junction remodelling leading to conduction blocked.

The conduction failure risk can be quantified by D_{min}, the minimal diffusion coefficient that supports stable conduction. In Figure 5 D_{min} was computed as percentage of the standard D for normal and channel remodelled strands with homo- and heterogeneous gap junction remodelling respectively. In both normal and channel remodelled tissues, tissue with heterogeneous gap junction remodelling required significantly larger D_{min} to support conduction than tissue with homogeneous gap junction remodelling.

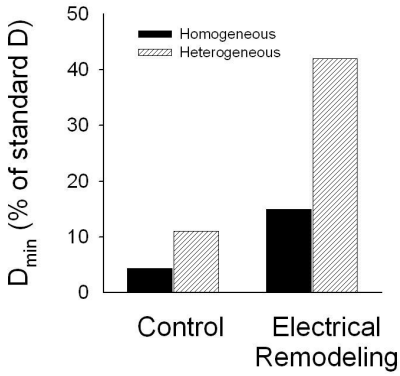

Figure 5. D_{min} (as percentage of the standard D) for atrial strands with homo- and heterogeneous gap junction remodelling to conduct excitation waves.

4. Discussion and conclusions

The main findings of this study are (1) AF-induced channel remodelling reduces atrial excitability and decreases atrial conduction velocity. Combined channel and gap junction remodelling decreases atrial conduction velocity significantly. This is different to a previous computational study that suggested a limited effect of AF on atrial conduction when only gap junction remodelling was considered [14]; (2) Both channel and gap junction remodelling have rate dependent effects on atrial conduction velocity. At low rates (stimulus interval SI > 270 ms), AF-induced channel or gap junction remodelling reduced CV significantly. At high rates (SI<270 ms), channel remodelling increased CV while gap junction remodelling reduced the CV. When combined, channel and gap junction remodelling reduced CV additively. (3) Channel remodelling enables atria to conduct excitation waves at a high rate, close to that during fibrillation. Such high rate excitation cannot propagate in normal or only gap junction remodelled tissue. This suggests that channel remodelling facilitates atrial fibrillation; (4) Gap junction remodelling, especially heterogeneous gap junction remodelling increases conduction failure risks that leads to conduction block. Conduction block is one of important factors necessary to generate re-entrant excitation wave leading to fibrillation.

Acknowledgements

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