Effect of sodium channel blockade on the 3-dimensional substrate of atrial fibrillation: a simulation study

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Background:

Anti-arrhythmic drugs, particularly sodium channel blocking agents, have been used as an important clinical compound for cardioversion of atrial fibrillation (AF). However, several experimental studies have revealed a reduction in cardioversion success rate after administration of sodium channel blockers in both animal models and patients in later stages of AF. The mechanisms underlying this efficacy loss are not fully understood.

Purpose:

In the present study, we investigated the loss of efficacy of Na-channel blockade to terminate atrial fibrillation (AF) in structurally remodelled atria, using a novel highly detailed human atrial computer model. We hypothesised that the possible explanation for the loss of efficacy is that structurally remodelled atria represent a higher degree of 3-dimensionality in the AF substrate. We assessed the effect of Na-channel blockade on endo-epicardial dissociation of electrical activity, transmural conduction, and AF stability at different degrees of structural remodelling.

Methods

We have developed a highly detailed human atrial computer model including all major endocardial bundle network structures and two to three layers of fibre orientations. Structural remodelling, sub-epicardial fibrosis in this study, was modelled by removing transverse conductivity for a random selection of model elements. Simulations were performed with 0, 50, 70% affected elements. We simulated 10 different episodes of AF, initiated at different locations, for each different group for a total of 30 simulations of 5 seconds each. We tested the effect of 60% Na^+-channel block in both AF termination success rate and conduction pattern complexity, quantified by number of waves and transmural conduction, in different degrees of fibrosis.

Results:

Na^+-channel block lost its efficacy to terminate AF with an increase in the degree of fibrosis. While in the absence of fibrosis Na+ channel block effectively reduced the number of fibrillation waves, at high degrees of fibrosis the number of waves was higher than before Na+ channel block. This was obviously due to the fact that a large excitable gap and an increase in the degree of endo-epicardial dissociation of electrical activity did not prevent the occurrence of a large number of breakthroughs (3D conduction).

Conclusion:

In the present study, we showed the efficacy loss of Na-channel blocker in AF termination in different stages of structural remodelling. Although, Na-channel block reduced the number of transmural conductions (BTs), the BT rates were still very high to support complex AF.

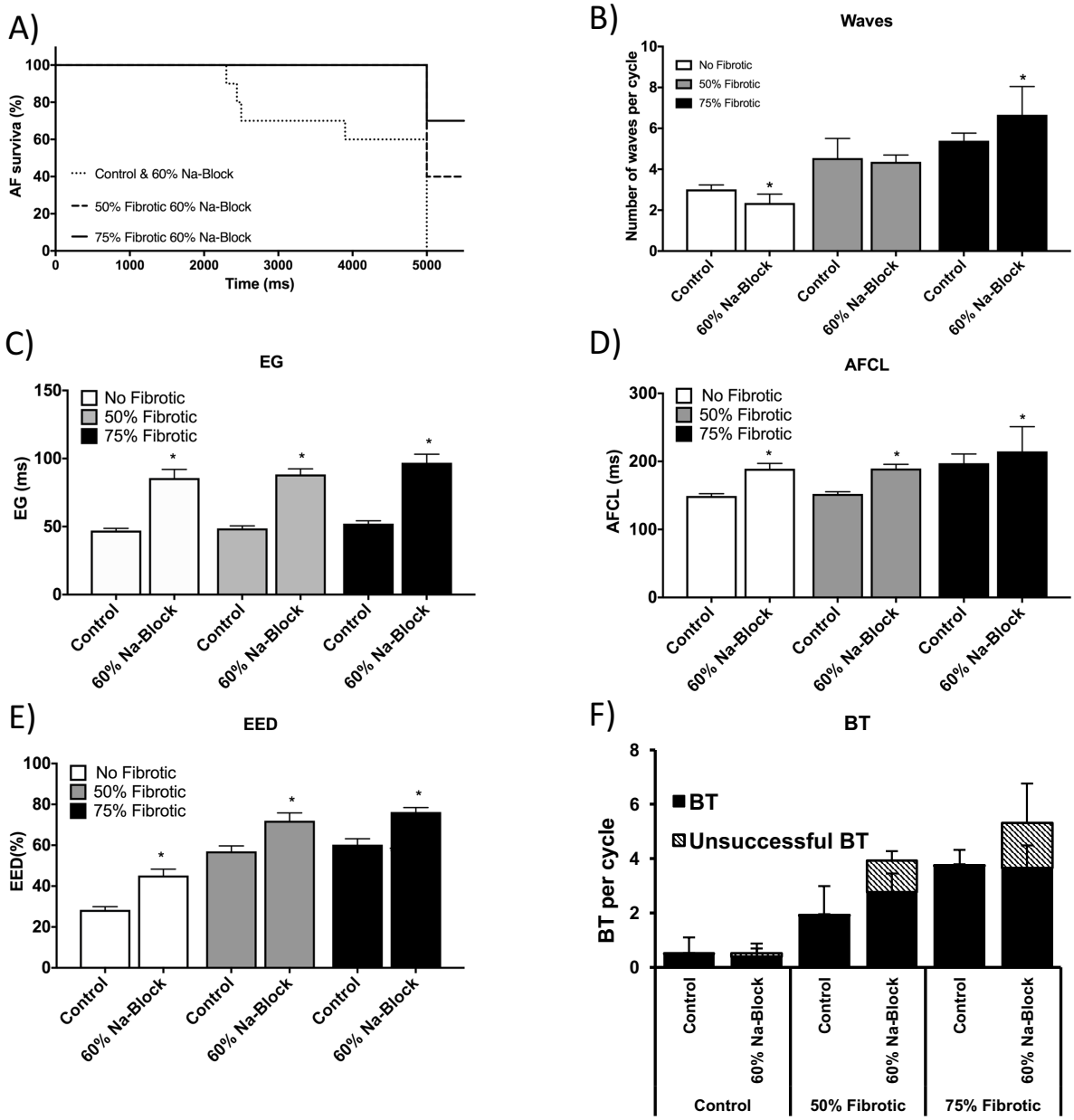

Figure: Na-channel block effect on AF conduction pattern. A) AF survival rate. B) Number of waves. C) Excitable gap (EG). D) AF cycle length (AFCL). E) endo-epicardial dissociation (EED). F) Number of successful and unsuccessful BTs.