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

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► To cite this version:

Ali Gharaviri, Mark Potse, Rolf Krause, Angelo Auricchio, Ulrich Schotten. Effect of sodium channel blockade on the 3-dimensional substrate of atrial fibrillation: a simulation study. EHRA Europace - Annual congress of the European Heart Rhythm Association, Mar 2018, Barcelona, Spain. 10.1093/europace/euy015.401 . hal-01910691

HAL Id: hal-01910691

<https://inria.hal.science/hal-01910691>

Submitted on 1 Nov 2018

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1 **Effect of Na⁺ - channel Blockade on the 3-Dimensional Substrate** 2 **of Atrial Fibrillation: A simulation study**

3 **Background:**

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

9 **Purpose:**

10 In the present study, we investigated the loss of efficacy of Na-channel blockade to terminate
11 atrial fibrillation (AF) in structurally remodelled atria, using a novel highly detailed human
12 atrial computer model. We hypothesised that the possible explanation for the loss of efficacy
13 is that structurally remodelled atria represent a higher degree of 3-dimensionality in the AF
14 substrate. We assessed the effect of Na-channel blockade on endo-epicardial dissociation of
15 electrical activity, transmural conduction, and AF stability at different degrees of structural
16 remodelling.
17

18 **Methods**

19 We have developed a highly detailed human atrial computer model including all major
20 endocardial bundle network structures and two to three layers of fibre orientations. Structural
21 remodelling, sub-epicardial fibrosis in this study, was modelled by removing transverse
22 conductivity for a random selection of model elements. Simulations were performed with 0,
23 50, 70% affected elements. We simulated 10 different episodes of AF, initiated at different
24 locations, for each different group for a total of 30 simulations of 5 seconds each. We tested
25 the effect of 60% Na⁺-channel block in both AF termination success rate and conduction
26 pattern complexity, quantified by number of waves and transmural conduction, in different
27 degrees of fibrosis.

28 **Results:**

29 Na⁺-channel block lost its efficacy to terminate AF with an increase in the degree of fibrosis.
30 While in the absence of fibrosis Na⁺ channel block effectively reduced the number of
31 fibrillation waves, at high degrees of fibrosis the number of waves was higher than before
32 Na⁺ channel block. This was obviously due to the fact that a large excitable gap and an
33 increase in the degree of endo-epicardial dissociation of electrical activity did not prevent the
34 occurrence of a large number of breakthroughs (3D conduction).
35

36 **Conclusion:**

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

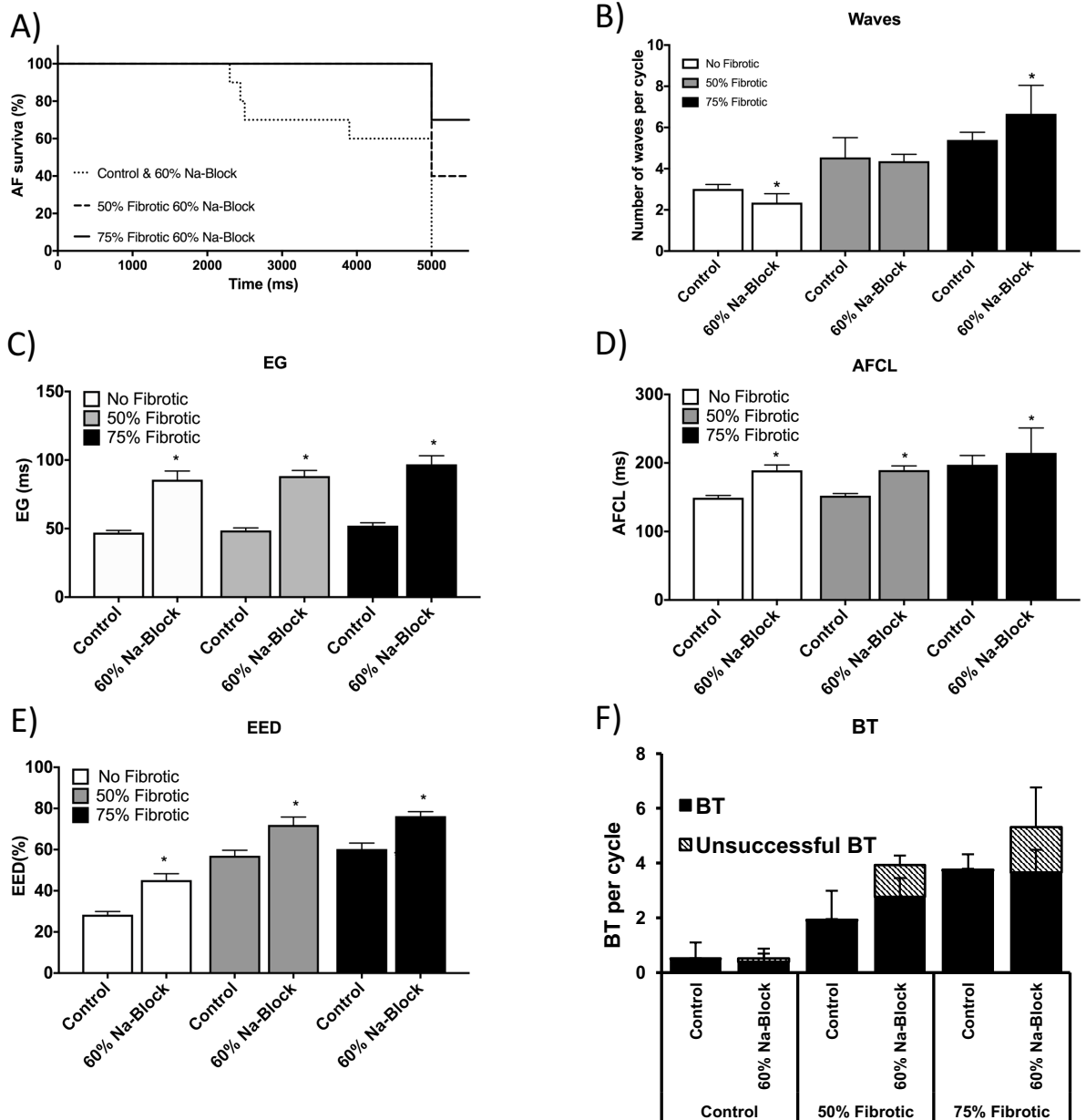


Figure: Na-channel block effect on AF conduction pattern. A) AF survival rate. B) Number of waves. C) Excitable gap (EG). D) AF cycle length (AFCL). E) endo-epicardial dissociation (EED). F) Number of successful and unsuccessful BTs.