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1 **Synergistic antiarrhythmic effect of inward rectifier current**
2 **inhibition and pulmonary vein isolation in a 3D computer model**
3 **for atrial fibrillation**

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26

27 **Abstract**

28 **Aims:** Recent clinical studies showed that antiarrhythmic drug (AAD) treatment and
29 pulmonary vein isolation (PVI) synergistically reduce atrial fibrillation (AF) recurrences after
30 initially successful ablation. Among newly developed atrial-selective AADs, inhibitors of the
31 G-protein-gated acetylcholine-activated inward rectifier current ($I_{K_{ACh}}$) were shown to
32 effectively suppress AF in an experimental model but have not yet been evaluated clinically.
33 We tested *in-silico* whether inhibition of inward rectifier current or its combination with PVI
34 reduces AF inducibility.

35 **Methods:** We simulated the effect of inward rectifier current blockade (I_K blockade), PVI,
36 and their combination on AF inducibility in a detailed 3-dimensional model of the human
37 atria with different degrees of fibrosis. I_K blockade was simulated with a 30% reduction of its
38 conductivity. AF was initiated using incremental pacing applied at 20 different locations, in
39 both atria.

40 **Results:** I_K blockade effectively prevented AF induction in simulations without fibrosis as
41 did PVI in simulations without fibrosis and with moderate fibrosis. Both interventions lost
42 their efficacy in severe fibrosis. The combination of I_K blockade and PVI prevented AF in
43 simulations without fibrosis, with moderate fibrosis, and even with severe fibrosis. The
44 combined therapy strongly decreased the number of fibrillation waves, due to a synergistic
45 reduction of wavefront generation rate while the wavefront lifespan remained unchanged.

46 **Conclusions:** Newly developed blockers of atrial specific inward rectifier currents, such as
47 $I_{K_{ACh}}$, might prevent AF occurrences and when combined with PVI effectively suppress AF
48 recurrences in human.

49 **Keywords:** Antiarrhythmic drug, Inward rectifier currents, Catheter ablation, Atrial
50 Fibrillation recurrence, *In-silico* study.

52 **What's new**

- 53 • We simulated the efficacy of inward rectifier current blockade and its combination
54 with PVI on prevention of AF initiation in different degrees of atrial fibrosis.
- 55 • The combination of inward rectifier blockade with PVI synergistically reduced the
56 likelihood of AF initiation in simulations with severe atrial fibrosis.
- 57 • The inward rectifier current blockade adjunctive to PVI strongly reduced the number
58 of fibrillation waves and new wavefront generation rate, while increasing the wave
59 size, and thereby strongly prevented AF induction.

60 **Condensed Abstract**

61 Continuation of antiarrhythmic drugs after catheter ablation has been shown to reduces AF
62 recurrences. We studied whether inhibition of inward rectifier current combined with catheter
63 ablation reduces AF inducibility in a realistic 3D computer model of human atria. We showed
64 that either inward rectifier current inhibition or PVI separately cannot significantly reduce AF
65 initiation likelihood in the simulations with severe atrial fibrosis, while their combination
66 can.

67

68

69 **1 Introduction**

70 Despite the development of pharmacological therapies for patients with atrial fibrillation
71 (AF), a large proportion of AF patients are not arrhythmia-free.¹ Pharmacological therapy is
72 less effective in non-paroxysmal AF patients than in paroxysmal AF patients, indicating the
73 significance of structural remodelling in the efficacy of pharmacological therapy. If the
74 treatment with antiarrhythmic drugs (AAD) fails, patients receive catheter ablation (CA) as a
75 second-line treatment.² CA is also associated with a rather disappointing long term outcome,
76 as after one year AF reoccurs in up to 30% of patients after PVI, despite proven complete PV
77 isolation supporting the presence of driver mechanisms of AF located outside the PV area.^{3,4}
78 The recent EAST trial stresses the need for early and effective rhythm control strategies⁵ and
79 combination of AADs with CA may be a strategy to achieve this. In a recent study,
80 Duytschaever et al. demonstrated that continuing previously ineffective treatment with AAD
81 after CA is associated with lower prevalence of atrial tachyarrhythmias after one year.⁶
82 However, the mechanisms underlying this synergistic inhibition of AF recurrences is not well
83 understood. Also, current AADs having potential side effects such as ventricular pro-
84 arrhythmia. For these reasons, atrial-selective AADs that do not affect ventricular conduction
85 or repolarization have been developed. Examples are blockers of the ultra-rapid inward
86 rectifier current (I_{Kur}), small-conductance Ca^{2+} -activated K^{+} -currents (SK), and the G-protein-
87 gated acetylcholine-activated inward rectifier current (I_{KAch}). A blocker of I_{KAch} (XAF-1407)
88 has recently been demonstrated to effectively suppress AF in an experimental equine model.⁷
89 Here, we tested whether inward rectifier current blockade reduces AF inducibility and
90 whether the combination of inward rectifier blockade with PVI prevents AF recurrences in a
91 computer model of human atria.

92 **2 Methods**

93 **2.1 Computational model of AF**

94 Computer simulations were performed on a highly detailed 3D model of human atria.⁸ The
95 model geometry was based on magnetic resonance imaging data of a subject with normal
96 atria with manually added anatomical structures and properties such as three layers of fibre
97 orientations, endocardial trabeculated network, Bachmann's bundle, wall thickness
98 heterogeneities, and left atrial appendage trabeculated network.⁸ Several studies have shown
99 that these structures have an essential role in AF initiation and maintenance.^{9,10} The model
100 consisted of approximately 5 million nodes spaced at 200 μ m.
101 Action potential propagation was simulated with a monodomain reaction-diffusion equation
102 using the Courtemanche-Ramirez-Nattel atrial cell model.¹¹ AF-induced changes in ionic
103 currents were incorporated by setting the conductivities for I_{to} , $I_{Ca,L}$, and I_{K1} at 40%, 35%, and
104 200% of their normal values, respectively.¹² Simulations were performed using the propag-5
105 software¹³ and run on a Cray XC50 supercomputer with GPU support.

106 **2.2 Modelling of inward rectifier current blockade**

107 The inward rectifier background current (I_{K1}) and the G-protein-gated acetylcholine-activated
108 inward rectifier current (I_{KAch}) show identical current-voltage relationships and are, therefore,
109 indistinguishable on the single cell level.¹⁴ Thus, both currents are adequately represented by
110 one total inward rectifier conductance in computer models. For this reason, inhibition of I_{KAch}
111 was simulated by reduction of this total inward rectifier current. The conductance of the
112 current was reduced by 30% resulting in a prolongation of the atrial action potential duration
113 by approximately 20ms, which is in the range of experimental studies.^{15,16}

114 **2.3 Distribution of tissue fibrosis**

115 The effect of structural remodelling was simulated by different degrees of fibrosis. The
116 conditions without, with moderate, and with severe fibrosis were modelled by setting 0%,
117 50%, and 70% of the elements in the model as fibrotic, respectively. Fibrotic elements
118 remained conductive along the fibre direction and isolated in the two transverse directions.
119 This modelling of atrial tissue fibrosis agrees with the experimental study by Spach et al. that
120 revealed loss of side-to-side electrical connections between atrial muscle bundles in fibrotic
121 atrial tissue.¹⁷ The fibrosis was distributed within the subepicardial layer, while the atrial
122 bundles remained intact. The spatial distribution of fibrosis was uneven, with patches or
123 island presenting higher degree of fibrosis. Such distribution was based on spatially
124 correlated, anatomy-tailored random fields.^{8, 18}

125 **2.4 Modelling of Pulmonary vein isolation**

126 In PVI simulations, two antral circumferential lines isolated the PV from the atria. Virtual
127 ablation lesions consisted of tissue volumes modelled by non-conductive elements.

128 **2.5 AF initiation in pre- and post-catheter ablations**

129 AF initiation likelihood was assessed by applying incremental pacing at 20 different locations
130 in both atria and compared between the control (no inward rectifier current inhibition and no
131 CA), inward rectifier current blockade (I_K blockade), PVI, and I_K blockade + PVI groups.
132 Pacing locations were selected based on reported possible sources of extra-PV ectopic focal
133 activity in AF patients, including the area between the PVs, left atrium, left atrial appendage,
134 right atrial appendage, coronary sinus, superior caval vein, inferior caval vein, and right
135 atrium.¹⁹ All pacing sites were located outside the ablated area. In each simulation, AF was
136 initiated by applying incremental pacing with a duration of 2 seconds at a selected pacing

137 site. In total, 14 stimuli were applied with the pacing cycle length gradually reducing from
138 280ms to 124ms. After the pacing period, the simulations were continued for another 3
139 seconds with no pacing.

140 **2.6 Definition of successful AF initiation**

141 The stimulation protocol outcome was analysed in terms of the type of self-sustained rhythm
142 after 2 seconds of stimulation. If no activation after pacing was noted, the initiation was
143 considered unsuccessful. Otherwise, a distinction between AF and atrial flutter (AFL) was
144 made, with the latter not being considered as successful AF initiation. AF and AFL
145 conduction patterns were differentiated by analysing the reconstructed 12-lead ECGs, as
146 described in detail in the supplementary material.

147 **2.7 Detection and tracking of fibrillation waves**

148 A fibrillation wave was defined as a contiguous volume in which all nodes had
149 transmembrane voltage above -60 mV. Wave size was defined as the number of model
150 elements within this contiguous volume. Both the number of waves and wave sizes were
151 calculated at each millisecond of simulated time.

152 Fibrillation waves were tracked in both time and space, as described in our previous study.²⁰

153 Briefly, the temporal dynamics of waves can be described by three events:

- 154 • Generation: appearance of a new wave either due to wave break or transmural
155 conduction.
- 156 • Fusion: the merge of two or more waves into one wave.
- 157 • Extinction: the extinction of a wave, due to encountering either a boundary or
158 unexcitable tissue.

159 **2.8 Statistics**

160 All statistical analyses were performed using GraphPad Prism software version 8.0. The
161 values are expressed as means \pm SD. Statistical tests were performed to compare the effect of
162 three parameters (fibrosis levels, I_K blockade, and PVI) in AF initiation rate, using two-way
163 ANOVA followed by post hoc Bonferroni test. A value of $P < 0.05$ was considered to be
164 significant.

165

166 **3 Results**

167 In total, 240 simulations were performed. The simulations consisted of 4 groups: control (no
168 interventions), inward rectifier current blockade (I_K blockade), PVI, and the combination of
169 inward rectifier current blockade and PVI (I_K blockade + PVI). Twenty simulations were
170 performed for each degree of fibrosis, resulting in the total of 60 simulations performed in
171 each group.

172 **3.1 AF initiation**

173 Figure 1A displays several action potentials recorded during simulated AF episodes in the
174 control and I_K blockade simulations. I_K inhibition caused prolongation of action potential
175 duration at 90% of repolarization (APD_{90}) from 119 ± 12.5 ms in control to 136 ± 10.4 ms.

176 Figure 2 depicts representative conduction patterns and corresponding ECG leads of I_K
177 blockade, PVI, and I_K blockade + PVI simulations under the condition of severe fibrosis. As
178 depicted in this figure, both I_K blockade and PVI failed to prevent AF initiation in severe
179 fibrosis simulations, while the combination rendered the atria uninducible.

180 Figure 3 shows initiation rates of atrial tachycardia in all simulation groups in the presence of
181 different degrees of fibrosis. The figure shows that in the absence of fibrosis, I_K blockade

182 caused a significant reduction in AF initiation likelihood when compared to control, either by
183 preventing initiation of AF or by transforming initiated AF into AFL. I_K blockade failed to
184 significantly reduce AF initiation rate in the simulations with moderate or severe fibrosis. In
185 PVI simulations, we observed significant reduction in AF initiation likelihood in the absence
186 or in the presence of moderate fibrosis when compared to control, while no significant
187 reduction was noted in the simulations with severe fibrosis. In the simulations that combined
188 PVI with I_K blockade, we observed a comparable reduction in AF initiation likelihood as in
189 PVI simulations in the absence of fibrosis or in the presence of moderate fibrosis. The
190 combination of I_K blockade and PVI further reduced AF initiation likelihood by at least half
191 in the simulations with severe fibrosis.

192 **3.2 Fibrillation pattern complexity**

193 Overall, a significant increase in AF cycle length was observed in all simulation groups when
194 compared to control, regardless of the fibrosis degree, as shown in Table 1. When compared
195 to control, no significant differences in the excitable gap were detected in any simulation
196 group (see Table. 1).

197 Examples of wave lifespans in control, I_K blockade, PVI, and PVI accompanied with I_K
198 blockade simulations with severe fibrosis are illustrated in figure 4A. An increase in the
199 fibrosis degree in control simulations led to a significant increase in fibrillation wave
200 generation rate, quantified as the slope of the fitted line to the wave lifespans, and therefore a
201 significant increase in AF conduction pattern complexity, quantified as the average number
202 of waves per cycle (Figure 4B & C). The increase in conduction pattern complexity was due
203 to the reduction of wave size and higher rate of new wavefront generation, while wavefront
204 lifespan medians remained unchanged (Figure 4D & E). In the simulations without fibrosis,
205 I_K blockade caused a significant reduction in the average number of waves per cycle, by

206 increasing the wave sizes and significantly reducing the rate of wavefront generation.
207 However, this effect of I_K blockade disappeared in the simulations with moderate and severe
208 fibrosis. PVI significantly reduced new wavefront generation rate in the simulations without
209 fibrosis as well as in the simulations with moderate fibrosis. Nevertheless, this effect faded in
210 PVI simulations with severe fibrosis. In I_K blockade combined with PVI simulations, the
211 synergistic interaction between the wave size enlargement caused by I_K blockade and the
212 reduction in atrial tissue mass caused by PVI further reduced the available space for
213 wavefront interactions. This resulted in significantly decreased rate of new wavefront
214 generation, and therefore in a smaller number of fibrillation waves.

215

216 **4. Discussion**

217 We investigated the isolated and combined effects of inward rectifier current blockade and
218 PVI on AF initiation in the presence of various degrees of atrial fibrosis. Both inward
219 rectifier blockade and PVI effectively reduced the rate of AF induction at low degrees of
220 atrial fibrosis but lost their efficacy in severely fibrotic atria. In the simulations with severe
221 fibrosis the combination of inward rectifier blockade and PVI effectively suppressed AF
222 recurrences, while either of the interventions was not efficient individually. The synergy
223 between both interventions resulted in reduction in the number of fibrillation waves. The
224 main underlying mechanism behind this effect was a reduction in the rate of new wavefront
225 generation, leaving the lifespan of fibrillation waves unaffected.

226 **4.1 Effect of inward rectifier current blockade and PVI in previous in-silico studies**

227 So far, several *in-silico* studies investigated the effect of different antiarrhythmic drugs
228 (single-channel or multiple-channel block) or CAs on AF initiation, perpetuation and
229 termination.^{21, 22}

230 Among the large variety of potassium channels expressed in human atria, the inward rectifier
231 currents I_{K1} and I_{KAch} play a significant role in AF perpetuation. Heterogeneous shortening of
232 the atrial effective refractory period caused by vagally modulated I_{KAch} channels are thought
233 to be the mechanism underlying vagally-induced AF.²³ Hence, inhibition of I_{KAch} may
234 minimize the effect of I_{KAch} modulations and could be a future therapeutic option for vagally-
235 induced AF.²³ Dobrev and colleagues have demonstrated that an increase of constitutively
236 active I_{KAch} strongly contributes to atrial action potential shortening in human persistent AF.¹⁴
237 Also I_{KAch} is active in atrial but not in ventricular cells so that inhibition of I_{KAch} is not
238 expected to prolong ventricular action potential. For these reasons inward rectifier currents
239 are an attractive target for antiarrhythmic treatment of AF.^{22, 24} Importantly, I_{K1} and I_{KAch} only
240 differ in their single channel conductance but their single cell level current-voltage
241 relationships are identical.¹⁴ Thus, both currents are adequately represented by the total
242 inward rectifier conductance in computer models.

243 The influence of inward rectifier current inhibition on AF initiation, termination, and
244 conduction pattern was investigated in several computational studies.^{21, 22} Sánchez et al.
245 demonstrated that inward rectifier inhibition led to higher arrhythmia organization by
246 enlarging wave sizes, increasing wave meandering, and reducing the number of secondary
247 wavelets.²⁴ These findings are in line with our results of inward rectifier current inhibition in
248 the atria without fibrosis in the present study. However, we observed significant efficacy loss
249 of inward rectifier current blockade in reducing the number of fibrillation waves and AF
250 termination or initiation in the presence of moderate or severe fibrosis.

251 The effectiveness of PVI to terminate AF in representative virtual atria was assessed in
252 several studies.²⁵ Recent proof-of-concept in-silico studies investigated the role of atrial
253 fibrosis in ablation failure using detailed patient-specific image-based models.²⁶ These
254 studies demonstrated that both the patient-specific degree and the distribution of fibrosis are a

255 determining factor in AF initiation and maintenance.²⁷ McDowell et al. demonstrated that
256 modelling of ablation lesions in the persistent rotor core meandering regions renders AF
257 uninducible.²⁷ Here, we simulated the combination of PVI and inward rectifier current
258 blockade and studied the mechanisms underlying the synergy between these two treatment
259 options on prevention of AF initiation.

260 **4.2 Synergism between inward rectifier inhibition and PVI to prevent AF recurrence**

261 The development of efficient therapy against AF remains an important unfulfilled clinical
262 need. Treatment with AADs has been considered as the first-line therapy² and recently has
263 been demonstrated to reduce major cardiovascular adverse events in patients with AF.⁵
264 However, the efficacy of AADs decreases with AF progression.² CA has been recognized as
265 an alternative therapeutic modality in AF treatment, which has been highlighted in several
266 studies to be more efficient than AAD therapy to prevent AF recurrences.²¹ Nevertheless, CA
267 results remain suboptimal, particularly in non-paroxysmal AF patients.²⁸ Recently, there has
268 been a growing interest in the effect of AAD continuation after CA.⁶ As reported in the
269 POWDER-AF trial, the AADs, despite being inefficient before ablation, are becoming
270 efficient in reducing AF recurrence after CA.⁶ The mechanisms underlying this synergy
271 between AADs and CA in AF recurrence prevention were so far not well understood.
272 Our simulations showed that either inward rectifier current inhibition alone or PVI alone can
273 significantly prevent initiation of AF only in the presence of no or moderate fibrosis, while
274 both became inefficient in the presence of severe fibrosis. When both strategies were
275 combined, little contribution to further reduction of AF inducibility in the simulations with no
276 or moderate fibrosis was observed. In severe fibrosis, inward rectifier blockade in
277 combination with PVI strongly reduced the number of fibrillation waves, increased their size
278 and strongly prevented successful AF induction. This effect was associated with significant

279 decline in the rate of new wave generation while wavefront lifespan remained unaltered. The
280 observed synergism might be explained by the fact that both PVI as well as the wavelength
281 prolongation by the inward rectifier blockade restrict the available space for wave-front-
282 wave-tail interactions which reduces the likelihood for wave break and generation of new
283 waves. Our results indicate that the newly developed inhibitors of $I_{K_{ACh}}$ have a potential to
284 show the observed synergism with PVI to prevent AF induction in a clinical setting.

355 **5 Limitations**

356 Inter-individual variabilities in anatomy, atrial size, fibre orientation, and wall thickness were
357 not considered in our study. Several clinical and simulation studies reported the effect of
358 variability in atrial geometry and the pattern of fibrosis on initiation of fibrillatory waves.^{26,}
359 ²⁹⁻³¹ Studying the effect of variations in the pattern of atrial fibrosis on AF inducibility is
360 certainly warranted. Although based on clinical data, the pattern of atrial fibrosis was
361 generated algorithmically in this study. We investigated the effect of inward rectifier current
362 inhibition, whereas several other currents have been shown to play an important role in AF
363 termination. Moreover, we did not investigate inhibition of multiple ion channels on AF
364 dynamics. Finally, heterogeneity in ionic parameters in our model has not been implemented
365 on purpose in order to avoid confounding factors.

366 **6 Conclusion**

367 This study shows that adding inward rectifier current inhibition to PVI caused a significant
368 reduction in AF recurrences even in the atria with severe fibrosis, whereas both treatments
369 alone failed to prevent AF initiation in severely fibrotic atria. This reduction in AF recurrence
370 rate is due to the synergistic effect of the two treatments to reduce the number of wavefront-
371 wavetail interactions, thereby lowering the rate of new wavefront generation and thus the
372 number of active fibrillation waves.

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381 **8 Conflict of interest**

382 Angelo Auricchio (AA) is a consultant to Boston Scientific, Backbeat, Biosense Webster,
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389 and YourRhythmics BV. The other authors have nothing to declare.

390

391

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486

487

488 **Figure 1:** A) Simulated action potentials during AF episodes in control and I_K blockade
489 simulations. Examples of simulated ECG in B) control and C) I_K blockade simulation.

490 **Figure 2:** Consecutive snapshots of conduction patterns and corresponding ECG leads (II,
491 V1, and V3) in I_K blockade, PVI, and I_K blockade combined with PVI simulations with severe
492 fibrosis. Black star indicates the stimulation point.

493 **Figure 3:** Atrial fibrillation (AF) and atrial flutter (AFL) initiation likelihood in control (no
494 I_K blockade and no PVI), PVI, and PVI + I_K blockade with different degrees of fibrosis.

495 **Figure 4:** Electrophysiological parameters. A) Examples of wave life spans in control, I_K
496 blockade, PVI, and PVI + I_K blockade simulations with severe fibrosis (the slope of the fitted
497 red line indicates the wave generation rate). B) Average number of waves per cycle. C)
498 Average wave sizes per cycle. D) Wave generation rate. E) Wave lifespan median.

499

500 **Table 1.** Atrial fibrillation cycle length (AFCL) and Excitable gap (EG) in simulation groups
 501 with different degrees of fibrosis.

| Simulation Groups Fibrosis | | Control | I _K blockade | PVI | PVI + I _K blockade | P Value |
|-------------------------------|-----------|-------------|-------------------------|-------------|-------------------------------|------------|
| | | | | | | |
| without | AFCL (ms) | 147.12 ±15 | 210.52* ±14 | 187.12*±13 | 202.12* ±15 | *P < 0.05 |
| | EG (ms) | 55.28 ± 4.3 | 59.2 ± 3.1 | 58.2 ± 2.9 | 57.9 ± 4.2 | P > 0.05 |
| moderate | AFCL (ms) | 152.28 ±18 | 224.06* ±16 | 192.28*±14 | 204.06*±16 | * P < 0.05 |
| | EG (ms) | 53.78 ± 3.1 | 58.77 ± 4.2 | 57.77 ± 3.3 | 57.77 ± 3.6 | P > 0.05 |
| severe | AFCL (ms) | 197.13 ±12 | 229.12* ±17 | 228.44*±11 | 219.12*±13 | * P < 0.05 |
| | EG (ms) | 54.64 ± 2.9 | 59.6 ± 3.8 | 57.6 ± 3.8 | 57.6 ± 3.1 | P > 0.05 |

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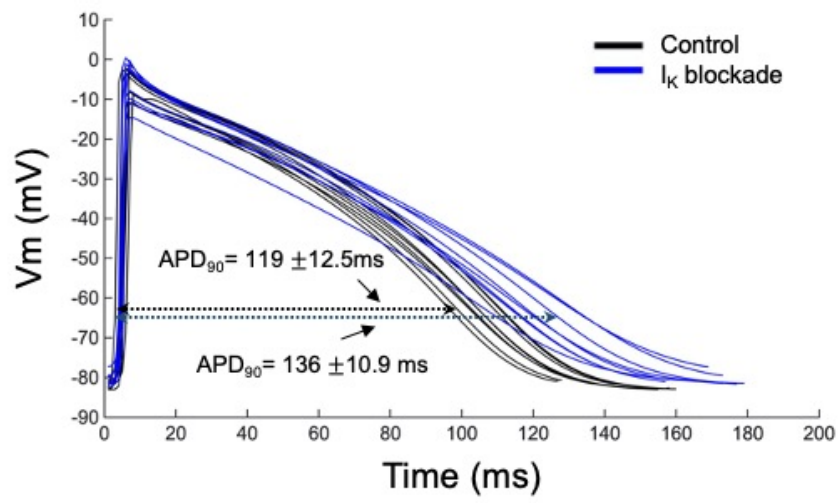
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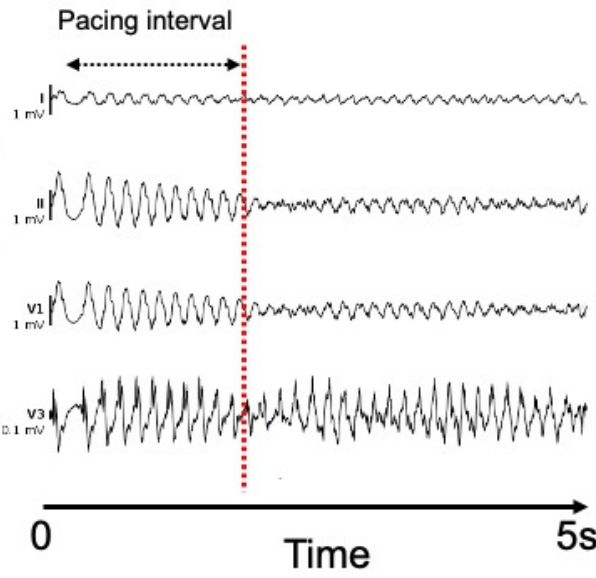
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Figure 1

A



B



C

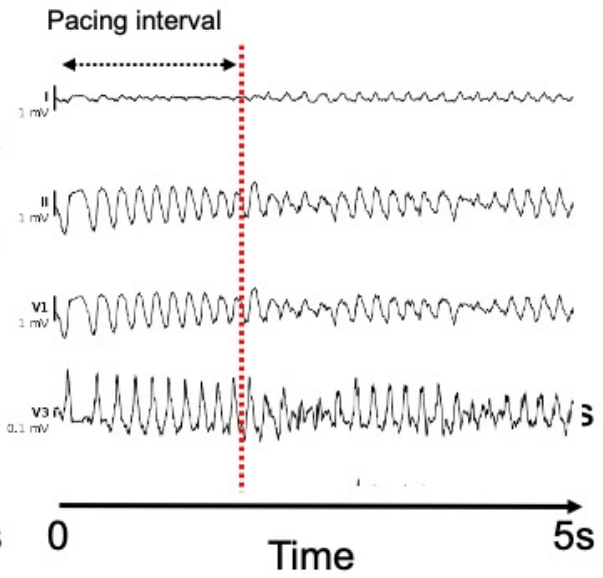


Figure 2

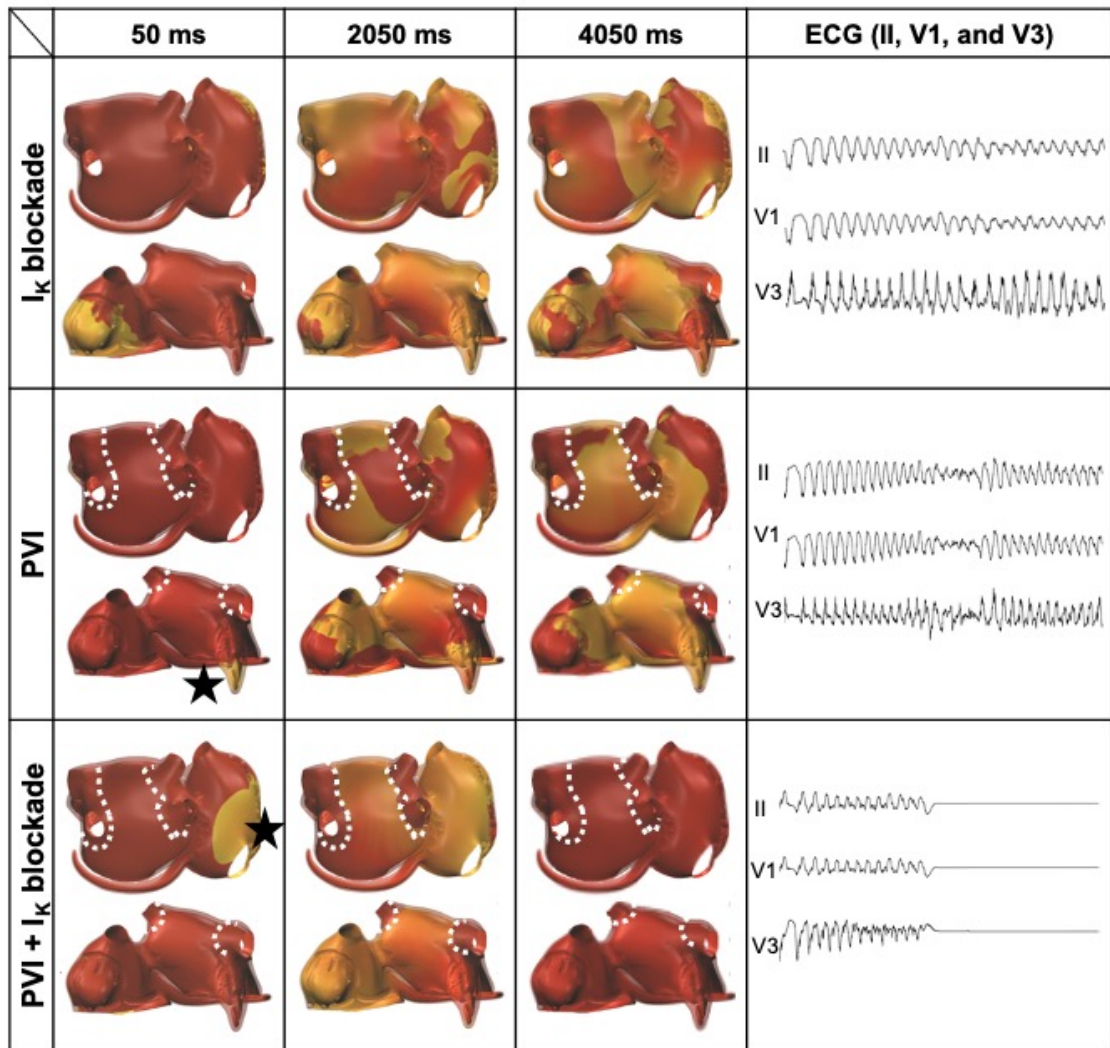


Figure 3

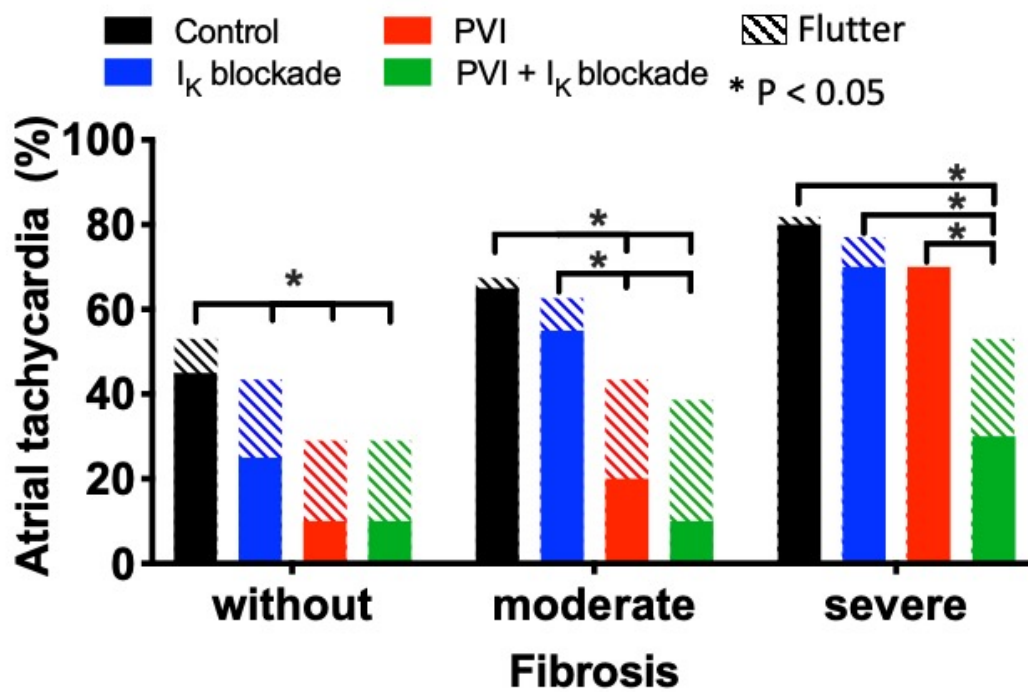


Figure 4

