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1 **Left atrial appendage electrical isolation reduces atrial fibrillation recurrences: a**
2 **simulation study**

3
4 **Gharaviri:** Atrial fibrillation recurrences after catheter ablation

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29 appendage electrical isolation, in-silico study.

30 **Non-standard Abbreviations and Acronyms:**

31 PV = Pulmonary vein

32 PVI = Pulmonary vein isolation

33 AF = atrial fibrillation

34 (persAF) = persistent atrial fibrillation patients

35 LAA = left atrial appendage

36 LAAI = left atrial appendage isolation

37 CA = catheter ablation

38

39 Pulmonary vein (PV) isolation (PVI) improves freedom from atrial tachyarrhythmia
40 recurrences in patients with paroxysmal and persistent atrial fibrillation (AF).¹ However, PVI
41 has a limited success rate in persistent AF patients (persAF) and ablation techniques
42 adjunctive to PVI isolating non-PV triggers remains an area of debate in these patients.¹
43 Recently, there has been a growing interest in the electrical and anatomical role of the left
44 atrial appendage (LAA) in triggering and sustaining AF, particularly in persAF or after
45 repeated AF ablation procedures.² Whether isolation of triggers originating from the LAA or
46 substrate modification caused by LAA isolation (LAAI) is the underlying mechanism for AF
47 recurrence prevention is still unknown.

48 We investigated the effect of LAAI in a structurally detailed model of the human atria,
49 extensively described previously³ (supplemental material). The model entails wall thickness
50 heterogeneities, endocardial trabeculated network, and a subepicardial layer with realistic
51 fiber orientations. **The material properties for the atria were set to produce an approximately**
52 **normal P-wave during sinus rhythm (Table S1).**

53 In total, 20 different pacing locations were selected in both atria based on reported possible
54 sources of extra-PV ectopic focal activity in AF patients⁴ (Figure).

55 In each simulation, AF was initiated by applying incremental pacing with the duration of 2
56 seconds at a selected pacing site. The pacing cycle length started with 280ms and gradually
57 reduced to 124ms. AF initiation likelihood was compared between control (no ablation) and
58 catheter ablation (CA) simulations with different degrees of fibrosis. CA simulations
59 included four groups: PV isolation (PVI), PVI plus linear lesions encircling the left atrial
60 posterior wall (BOX), PVI plus LAA circumferential isolation (PVI + LAAI), and BOX +
61 LAAI. Virtual ablation lesions consisted of tissue volumes modeled by non-conductive
62 elements. The outcome of the stimulation protocol was analyzed in terms of the type of self-
63 sustained rhythm after 2 seconds of stimulations. If no activity was observed, the initiation
64 was considered unsuccessful. Otherwise, a distinction between AF and atrial flutter (AFL)
65 was made (supplemental material), with the latter being considered unsuccessful.

66 The spatial distribution of fibrosis was uneven, with patches or islands presenting higher
67 degree of fibrosis (Figure S1).³ Simulations were performed without fibrosis, with moderate
68 fibrosis, and severe fibrosis, in which 0%, 50%, and 70% of elements were fibrotic.³

69 In total, 300 simulations were performed. Each simulation group entails 60 simulations (20
70 simulations for each fibrosis degree).

71 In control simulations, an increase in the fibrosis degree led to a significant increase in AF
72 initiation likelihood. In simulations without fibrosis or with moderate fibrosis (which may
73 represent paroxysmal AF patients), PVI and BOX caused a significant reduction in AF
74 initiation likelihood, either by preventing initiation of fibrillation or by converting AF into
75 AFL (Figure). In contrast, in PVI and BOX simulations with severe fibrosis (which may
76 represent persAF) we observed no significant reduction in AF initiation likelihood. In
77 simulations with LAAI on top of PVI or BOX, we observed a comparable reduction in AF

78 initiation likelihood as in PVI only or BOX simulations in the absence of fibrosis or in the
79 presence of moderate fibrosis. In severe fibrosis, adding LAAI to PVI or BOX further
80 reduced AF initiation likelihood by at least one third.

81 An increase in fibrosis degree in control simulations led to a significant increase fibrillation
82 wave generation rate and therefore a significant increase in AF conduction pattern
83 complexity, quantified as number of waves per cycle (Figure). In simulations without fibrosis
84 or with moderate fibrosis, CAs caused a significant reduction in fibrillation wave generation
85 rate and AF conduction pattern complexity. In contrast, in severe fibrosis simulations, a
86 significant reduction in wave generation rate and AF pattern complexity was only observed in
87 simulations with LAAI plus PVI or BOX.

88 In our control group, the averaged AF cycle length (AFCL) was 149ms, value previously
89 reported in AF patients. In simulations without fibrosis or with moderate fibrosis, CAs caused
90 a significant AFCL prolongation (Table S2). In severe fibrosis simulations only the presence
91 of LAAI concomitant with CAs could significantly increase AFCL.

92 The simulations were performed on a single atrial geometry and inter-subject variability
93 could have effects on simulations results. However, the in-depth study of the atrial anatomy
94 effect on AF initiation is beyond the scope of this study.

95 We modelled LAAI and investigated its effect on AF recurrences in the presence of different
96 degrees of fibrosis. As presented, adding LAAI to either PVI or BOX significantly lowered
97 AF recurrence rate in severe fibrosis simulations, which is consistent with clinical studies
98 mentioning the significant effect of LAAI in lowering AF recurrence rates in persAF.²

99 Finally, we could demonstrate that the mechanisms underlying AF initiation prevention in the
100 presence of LAAI is not due to isolating triggers in LAA, but rather related to the reduction
101 of AF conduction pattern complexity as a result of substrate modification due to LAAI.

102

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140 **Figure 1.** A) Catheter ablation patterns and pacing points (pacing locations located outside of
141 ablated area were indicated by black stars and the pacing location within the ablated area was
142 indicated by yellow). B) AF and AFL initiation likelihood in control and catheter ablation
143 simulations with different degrees of fibrosis. C) Number of waves per cycle. Wave life span
144 and wave generation rate (the slope of fitted line) in D) control E) PVI F) PVI + LAAI
145 simulations with sever fibrosis.

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