In-Silico Trials Guide Optimal Stratification of Atrial Fibrillation Patients to Catheter Ablation vs Pharmacological Medication: The i-STRATIFICATION Study

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Abstract

Persistent atrial fibrillation (AF) patients show a 50% recurrence after pulmonary vein isolation (PVI), and no consensus is established for following treatment. The aim of our i-STRATIFICATION study is to provide evidence for optimal stratification of recurrent AF patients to pharmacological versus ablation therapy, through in-silico trials in 800 virtual atria. The cohort presents variability in anatomy, electrophysiology, and tissue structure (low voltage areas, LVA), and is developed and validated against experimental and clinical data from ionic currents to ECG. AF maintenance is evaluated prior- and post-PVI, and atria with sustained arrhythmia after PVI are independently subjected to seven state-of-the-art treatments for AF. The results of the i-STRATICICATION study show that the right and left atrial volume dictate the success of ablation therapy in structurally-healthy atria. On the other hand, LVA ablation, both in the right and left atrium, is required for atria presenting LVA remodelling and short refractoriness. This atrial refractoriness, mainly modulated by L-type Ca^{2+} current, I_{CaL}, and fast Na^+ current, I_{Na}, determines the success of pharmacological therapy. Therefore, our study suggests the assessment of optimal treatment selection using the above-mentioned patient characteristics. This provides digital evidence to integrate human in-silico trials into clinical practice.

1. Introduction

Catheter ablation is the most effective therapy for preventing arrhythmia recurrence in patients with paroxysmal atrial fibrillation (AF) [1]. With most ectopic triggers originating in the pulmonary veins, pulmonary vein isolation (PVI) has emerged as the cornerstone of ablation therapy. However, challenges remain for persistent AF (PeAF), where patients experience 40-50% recurrence after PVI [2]. Furthermore, attempts to target the substrate that maintains fibrillation in several clinical trials, such as posterior wall isolation (PWI) [3], ablation of complex fractionated electrograms [2] and of low voltage areas (LVA) [4], have failed to improved AF freedom compared to PVI alone.

Novel ablation approaches, namely, MiLine (ablation of the anterior mitral line [5]) and Marshall-Plan (sequential elimination of the coronary sinus and vein of Marshall bundles, PVI, and empirical right and left atrial lines [6]), have shown promising results in multicentre retrospective and prospective studies, respectively. While effective and approved to be tested in larger trials, these strategies rely on extensive ablation lesions, potentially over-treating patients. Therefore, a major challenge remains the patient-specific identification of optimal treatment, namely extensive versus minimal substrate modification, LVA ablation or PVI plus antiarrhythmic drug therapy.

Due to their multiscale nature and scalability, human in-silico trials can assist in identifying individual patient characteristics to guide optimal therapy selection in large patient cohorts. Thus, the aim of our i-STRATICICATION study is to provide evidence for optimal stratification of recurrent PeAF patients to pharmacological versus ablation therapy, through in-silico trials in 800 virtual patients with state-of-the-art AF treatments.

2. Methods

2.1. Study design

The i-STRATIFICATION study evaluated AF maintenance in 800 virtual atria prior- and post-PVI. Atria presenting sustained arrhythmia after PVI were independently subjected to cutting-edge treatments for AF (*ablation arm:* PWI, MiLine, Marshall-Plan, and LVA; *antiarrhythmic drug arm:* vernakalant and amiodarone; **Figure 1**). This framework served to build a decision algorithm, based on key patient characteristics, that guided patient stratification to optimal AF management. Both the current framework and the decision algorithm highlight the potential for direct translation of human in-silico trials into a clinical setting.
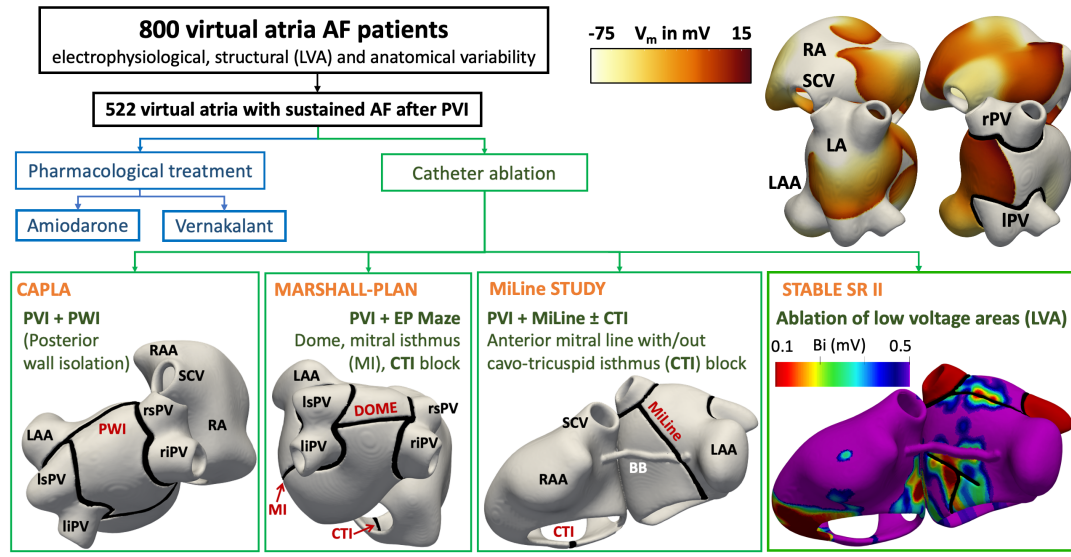
Figure 1.
Design of the i-STRATIFICATION study: Virtual atria presenting sustained arrhythmia after PVI are independently subjected to two antiarrhythmic drugs and five catheter ablation approaches, simulating recently published and ongoing randomized clinical trials: CAPLA [3], Marshall-Plan [6], MiLine [5], and STABLE-SR-II [4].

2.2. Study population

The virtual cohort consisted of 800 human atria with variability in anatomy, electrophysiology, and tissue structure. In line with clinical observations [4], half of the population was modelled without LVA (areas of bipolar voltage lower than 0.5 mV in sinus rhythm, **Figure 1**). The other half expressed 15% left and right atrial LVA [7].

Cohort of 400 structurally-healthy atria (LVA<1%): Electrophysiological variability was introduced by creating a population of 40 atrial cardiomyocyte models, calibrated with recordings from PeAF patients [8]. To study anatomical variability associated with AF recurrence [9], 10 atrial anatomies (right and left atrium, 127±51 mL and 105±39 mL, respectively; mean±SD) were chosen. The cohort of 400 patients was created combining the 40 single cell models with the 10 anatomies (**Figure 2**).
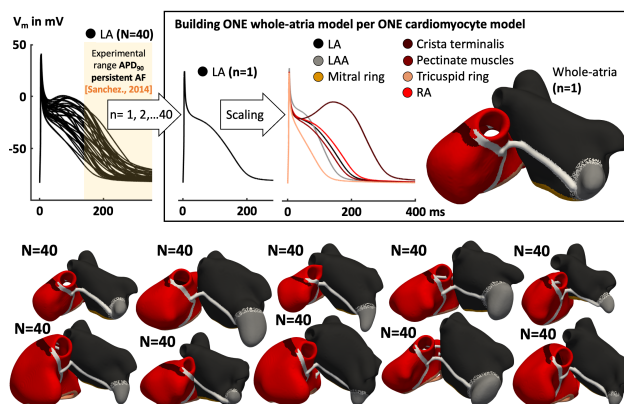

Figure 2. Development of 400 structurally-healthy atria with anatomical and electrophysiological variability, both inter- and intra-atria. RA-LA: Right and left atrium. LAA: LA appendage.

Cohort of 400 structurally-remodelled (15% LVA) atria: The cohort was extended to 800 patients by adding LVA into each of the 400 structurally-healthy atria. To identify atrial regions more likely to undergo structural remodelling, probabilistic LVA maps were created using the bipolar voltage maps of 20 PeAF patients undergoing PVI. The most probable areas were assigned to be LVA until 15% [7] of the left and right atrium was remodelled (**Figure 1**). LVA were simulated as previously [9].

2.3. AF induction

AF was induced in the 800 virtual atria by imposing spiral wave re-entries as the initial conditions of the simulation, and AF dynamics were analysed for 7 s of activity [10]. Atria with sustained AF (>7 s) underwent PVI, and the AF induction protocol was newly assessed.

2.4. Intervention

Virtual patients with uninterrupted arrhythmia after PVI were independently subjected (i.e., underwent every single treatment separately) to five ablation strategies and two antiarrhythmic drugs (**Figure 1**). Drug action was simulated as a simple pore-block model, with the percentage of ionic current block shown in **Table 1**.

Table 1. Ionic current block (%) exerted by the antiarrhythmic drugs amiodarone (A) and vernakalant (V).

	I_{Kur}	I_{Kr}	I_{to}	I_{K1}	I_{Ks}	I_{CaL}	I_{NaK}	I_{NCX}	I_{Na}
A	-	65	30	50	50	-	25	50	40
V	60	60	60	-	-	20	-	-	70

Ablation was simulated by removing cells from the atrial mesh. The resulting lesions reproduced those of the associated clinical studies with two modifications. Firstly, MiLine [5] was additionally simulated considering a cavo-tricuspid-isthmus (CTI) block to prevent right atrial flutter (MiLine+CTI). Secondly, LVA ablation was applied in two steps: only isolating LVA in the left atrium [4] and together with a right atrial LVA ablation.

The three-dimensional monodomain equation of the transmembrane voltage was solved using the high-performance open-source software MonoAlg3D [11].

3. Results and discussion

3.1. Primary outcomes

After applying PVI, sustained arrhythmia occurred in 522 (65%) virtual atria (243 and 279 with LVA<1% and LVA of 15%, respectively). In this cohort, additional PWI had no beneficial impact, in agreement with CAPLA [3], and arrhythmia only stopped in 0.02% atria. MiLine and MiLine+CTI prevented 54% and 75% of the 522 AF cases, respectively, similar to a 70% efficacy reported in [5]. Marshall-Plan yielded a 67% freedom from arrhythmia, comparable to 72% observed in [6]. Finally, LVA ablation was applied in the 279 atria with LVA remodelling, and 81% prevention was observed. Regarding the antiarrhythmic drug arm, both amiodarone and vernakalant had a success rate of 57%, as reported clinically [12].

3.2. Antiarrhythmic drug arm

The ionic current substrate of the atria greatly determined the response to pharmacological treatment. However, amiodarone efficacy was lower in structurally-remodelled atria (66% and 50% with LVA<1% and 15% LVA, respectively). In the absence of LVA, amiodarone was effective in atria with higher L-type Ca^{2+} current (I_{CaL}) density (0.13±0.03 vs. 0.09±0.02 S/mF; responders vs. non-responders). After LVA remodelling, amiodarone success was dependent on low Na^+/K^+ pump (0.64±0.14 vs. 0.75±0.9 A/F), thus low excitability. On the other hand, vernakalant efficacy was similar in both groups (56% and 58% with LVA<1% and 15%, respectively) and depended on the fast Na^+ current (I_{Na}) density (5.7±1.1 vs. 9.1±1.1 S/mF; responders vs. non-responders).

3.4. Catheter ablation arm

Cohort of 243 structurally-healthy atria (LVA<1%) with arrhythmia post-PVI: In structurally-healthy atria, ablation efficacy was determined by the atrial volumes. After PVI, AF proportion was directly proportional to the right atrial volume (increase of 0.21%/mL) and occurred in 106 (43%) atria. Atypical flutter was more common (57%), emerging around the rings of the isolated veins. Similarly, PWI created a favourable substrate for flutter to appear around the ablated box. This happened in 123 (51%) cases, with 110 (45%) atria presenting AF and 10 (4%) being arrhythmia-free. Thus, while PWI could be effective in isolating focal activity within the posterior wall, it failed to prevent arrhythmias emerging from other atrial regions. In this sense, Marshall-Plan and MiLine+CTI were preferable strategies. Both ablation approaches blocked anatomic structures recognized as AF perpetuators [6], but compared to Marshall-Plan, AF episodes were greatly reduced by

MiLine+CTI (25 (10%) and 6 (2%), respectively). Marshall-Plan was effective in small left atria, but AF proportion increased proportionally to the left atrial volume (0.15%/mL). This was due to a preferential location of rotors in the anterior wall of the left atrium, which were prevented by MiLine+CTI (**Figure 3**). After applying the latter, AF could sustain only for large right atria (>170 mL). The importance of right atrial ablation was observed comparing the outcomes of MiLine vs. MiLine+CTI (96 (40%) vs. 6 (2%) AF cases, respectively). Indeed, increased AF incidence occurred after MiLine when the right atrial volume was higher than 90 mL.
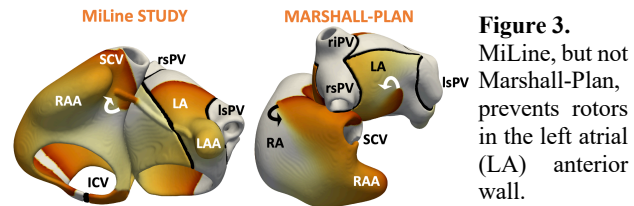
Figure 3. MiLine, but not Marshall-Plan, prevents rotors in the left atrial (LA) anterior wall.

Cohort of 279 structurally-remodelled atria (15% LVA) with arrhythmia post-PVI: The efficacy of empirical ablation approaches dropped substantially with the presence of LVA (e.g., 75% vs. 61% freedom after Marshall-Plan for LVA<1% vs. 15% LVA). An increase in AF complexity owed to a higher amount of pathological conduction patterns located in LVA. Thus, only LVA ablation was able to prevent arrhythmia (**Figure 4**).
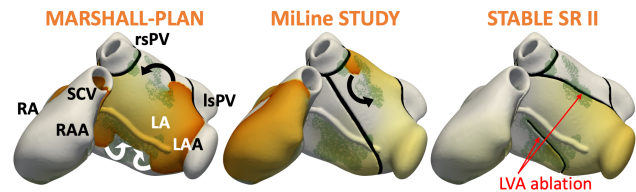
Figure 4. Pathological conduction patterns (i.e., fractionation, rotors) within LVA are only terminated after LVA ablation.

Nevertheless, rotors only localized in LVA for atria with short refractoriness, due to very low I_{CaL} density (0.08±0.02 S/mF). Atria with higher I_{CaL} (0.14±0.03 S/mF) responded to empirical ablations, following the same principles as structurally-healthy atria. Even after applying LVA ablation in the left atrium, AF proportion increased with increasing right atrial volume (0.16%/mL). From the 54 (20%) cases not prevented by left atrial LVA ablation, 38 (70%) showed pathological conduction patterns within right atrial LVA. These subjects presented bigger right atria (>90mL) and shorter wavelength, due to reduced I_{Na} and rapid delayed outward rectifier K^+ current (I_{Kr}) densities (5.4±1.6 and 0.03±0.006 S/mF, respectively). Additional right atrial LVA ablation prevented the arrhythmia. The remaining 16 (30%) atria, characterized by higher I_{Na} and I_{Kr} (9.3±0.8 and 0.04±0.002 S/mF), exhibited rotors in the crista terminalis. These atria were free from arrhythmia after additional pharmacological treatment (ablating the crista was not considered).

4.   Conclusion and clinical implications

In conclusion, the atrial volumes ruled ablation success, thus optimal strategy selection in structurally-healthy atria. On the other hand, LVA ablation, both in the right and left atrium, was required for atria presenting LVA remodelling and short refractoriness. This atrial refractoriness, mainly modulated by I_{Na} and I_{CaL}, additionally determined the success of pharmacological therapy. Therefore, our study suggests to assess optimal treatment selection using the following patient characteristics: right and left atrial volumes, I_{Na} and I_{CaL} densities, and the extent of LVA. As shown in **Figure 5**, our in-silico trials have inferred a decision algorithm for patient stratification. It provides digital evidence to directly translate and integrate human-based modelling and simulation into clinical practice.
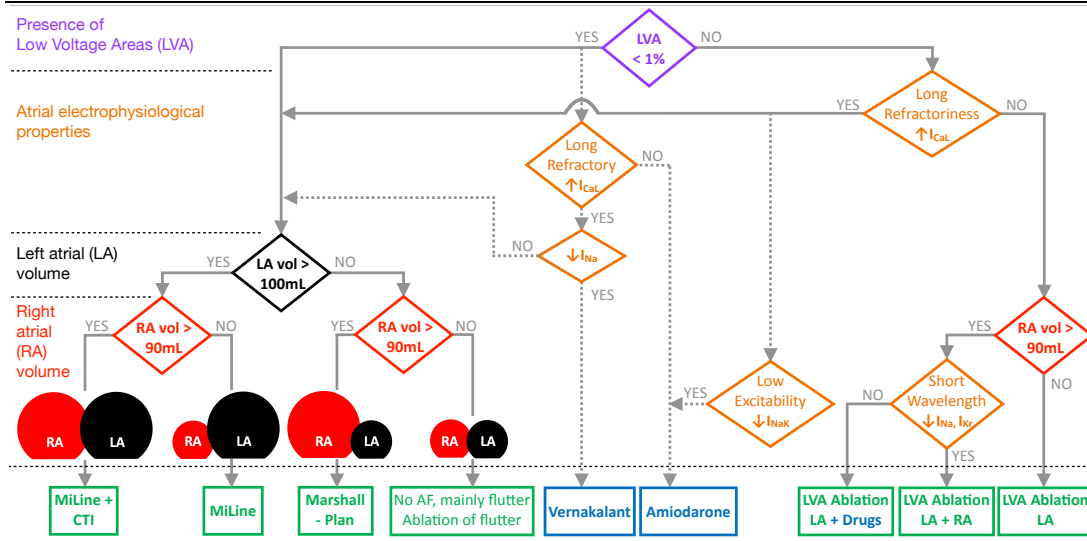

Figure 5. Decision algorithm for optimal stratification of persistent atrial fibrillation patients to catheter ablation or anti-arrhythmic drug therapy.

Pharmacological treatment is presented with dashed lines since its selection is also influenced by possible patient's heart disease [13].

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