The Impact of Anatomical Variability on Atrial Fibrillation Dynamics: A Novel Personalized In-Silico Approach

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Abstract

Aims: *We aimed to assess the effects of anatomical variability on atrial fibrillation (AF) initiation and complexity through a novel patient-specific model strategy incorporating detailed atrial structures.* ***Methods:*** *Personalized models from 10 patients undergoing AF ablation were created by combining atrial anatomies extracted from magnetic resonance imaging with detailed structures mapped from a reference model. Pectinate muscles, Bachmann's bundle, coronary sinus, and fiber orientations were mapped from the reference to the patient models using an extended implementation of the universal atrial coordinates algorithm. All models had identical electrophysiological properties. We assessed the inducibility of AF and macroreentrant tachycardia in each model after incremental pacing (20 sites). For AF, complexity was analyzed via the functional reentry formation/termination rates and the estimated number of simultaneous reentries using the renewal theory.* ***Results:*** *AF initiation rates did not vary significantly across models (50.0% [IQR: 36.2%-53.8%], p=0.43). While reentry termination rates were similar across models, formation rates varied significantly among patients (1.28 [0.66; 1.68] %/ms, $p<0.01$), leading to variability in the number of co-existing reentries and in the resulting AF complexity.* ***Conclusion:*** *Anatomical differences alone caused inter-patient variability in the AF susceptibility and complexity.*

1. Introduction

Personalized computer models of the atrial electrophysiology are relevant tools for investigating the behavior of atrial fibrillation (AF) in individual patients, thus helping to improve our understanding of AF pathophysiology and investigate the effect of treatment strategies [1].

The individual atrial anatomy may play an important role in the vulnerability and complexity of AF [2]. Most models include personalized anatomies tailored after imaging data. At the same time, they often simplify important structures that can significantly impact arrhythmogenesis, and assume homogeneous wall thickness and continuous contact between the muscular layers, without representing areas with structural discontinuities, such as the right atrial (RA) lateral wall and the left atrial (LA) appendage (LAA) [3].

Including such intra-atrial structures in models is not trivial due to limitations in spatial resolution of current imaging technology[1]. In previous work by our group, we addressed this issue by manually introducing these structures following rules derived from population-level histological data [4]. However, this approach is time consuming and does not scale up to routinely generate personalized models.

In the present study, we proposed a framework to automatically generate personalized atrial models that include variations in wall thickness and endo-epicardium contact. We enhanced the gross atrial anatomy obtained from segmented MRI images with detailed intra- and inter-atrial structures by using a reference model and a common anatomy-based coordinate system. Through a cohort of personalized models generated with this approach, we evaluated the impact of anatomical differences and presence of inter-individual differences on the AF initiation rates and the resulting AF complexity of initiated episodes.

2. Methods

2.1. Building personalized atrial models

Personalized models were generated for 10 patients undergoing AF ablation (local ethics committee approval

protocol reg. HCB/2022/1186) by following a three-step process: first, the LA and RA anatomies were extracted from the MRI data; then, the patient anatomies and our previously developed reference models were mapped to a common coordinate system; finally, structures below the MRI resolution were mapped to the individual anatomies from the reference model using the common coordinates [5, 6].

LGE-MRI was used to obtain the patient atrial anatomies. A mid-wall estimation of the atrial geometry was obtained by segmenting the MRIs with the ADAS 3D software (Adas3D Medical SL, Barcelona, Spain). Openings were manually added at the pulmonary veins, tricuspid and mitral valve rings, coronary sinus (CS), and superior and inferior vena cava. Furthermore, the cells corresponding to the LAA were manually annotated.

We used our previously developed model as a guide to include atrial structures not observed in the MRIs [4]. The model was built by deriving rules from the available literature on the atrial anatomy to place intra-atrial structures such as the pectinate muscles in the RA, LAA bundle networks, inter-atrial structures such as the Bachmann bundle, posterior connections, and CS, and endocardial and epicardial fiber directions. In that model, pectinate muscles and posterior connections were represented as tubes determined by splines indicating their positions and a given cross-section to obtain varying thickness depending on the bundle. Fiber orientations were represented as splines included in the corresponding layer (endo- or epicardium). The CS and Bachmann bundle were represented as meshes combined with the main atrial envelopes.

To enable the inclusion of these structures on the patient geometries, we employed the universal atrial coordinates (UAC) proposed by Roney and colleagues [5, 6] with two modifications to enable mapping across the atrial wall thickness and minimize distortions. First, we included a third coordinate to the UAC system representing the distance from the atrial wall along the normal direction. This coordinate was used when transferring the atrial structures from the reference to the patient models. Distances and cross-sections were adjusted according to the change in LA/RA model with respect to the reference model: $D_{pat} = D_{ref}\sqrt{V_{pat}/V_{ref}}$, where D_{ref} and V_{ref} are the distance from the atrial wall and atrial volume in the reference model, and D_{pat} and V_{pat} are the corresponding quantities in the patient models.

We also introduced a separate coordinate system for the LAA to reduce distortions when converting to the two-dimensional UAC coordinate system. This LAA-specific system included an apical coordinate, measured along the axis from the LAA opening to its tip, and a radial coordinate, defined between two boundaries: the shortest path from the tip to the LAA opening point nearest the mitral valve and the shortest path from the tip to the LAA opening point nearest the left superior pulmonary vein. Like in the original UAC, openCARP was used to compute the Laplace solution and define these coordinates.

After computing the modified UACs for the reference and patient anatomies, the atrial structures present in the reference model were included on the patient anatomy by using the Blender software with its native Python support for automatization. Subsequently, these structures were combined into a single volumetric mesh using a dedicated software suite [4]. The meshes of the personalized models are structured grids comprising of approximately 5 million cubic elements with a length of 0.2 mm. All the models were assigned identical action potential characteristics, as previously described [4].

2.2. Assessing AF inducibility and complexity in the personalized models

We performed 20 AF initiation attempts with incremental pacing (280-124 ms cycle length) on each patient model and the reference model. We ran simulations using propag-5 for a period of up to 10s, or until spontaneous termination [4]. Initiated simulations could be either AF, sustained by a combination of transmural breakthroughs and reentries, or a macro-reentrant atrial tachycardia (MRAT), where a macro-reentry is present around anatomical structures. The differentiation between AF and MRAT was made by tracking functional reentries, which are absent in the case of MRATs, through phase analysis of the simulated transmembrane potentials.

The complexity of AF in the simulation was assessed by the formation (λ_f) and destruction rates (λ_d) of functional reentries under the framework of the renewal theory [7]. These rates are constant properties of a fibrillatory episode and can help determine the expected number of coexisting reentries ($N = \lambda_f/\lambda_d$), associated with the AF complexity. Inter-formation times and the duration of each reentry were used to estimate λ_f and λ_d, respectively, through maximum likelihood data fitting [7].

We compared AF and supraventricular tachycardia (SVT, including AF and MRAT) initiation rates among models with a chi-square test. ANOVA (post-hoc: Dunn's test) was used to compare λ_f and λ_d. Statistical significance was set at 0.05.

3. Results

The patient cohort had a median LA volume of 101.5 ml [72.5 ml; 105.9 ml] and a median RA volume of 100.5 ml [82.5 ml; 113.3 ml]. Examples of the personalized model anatomies are displayed in Fig. 1A, where the structures added based on the reference model are highlighted in distinct colors.

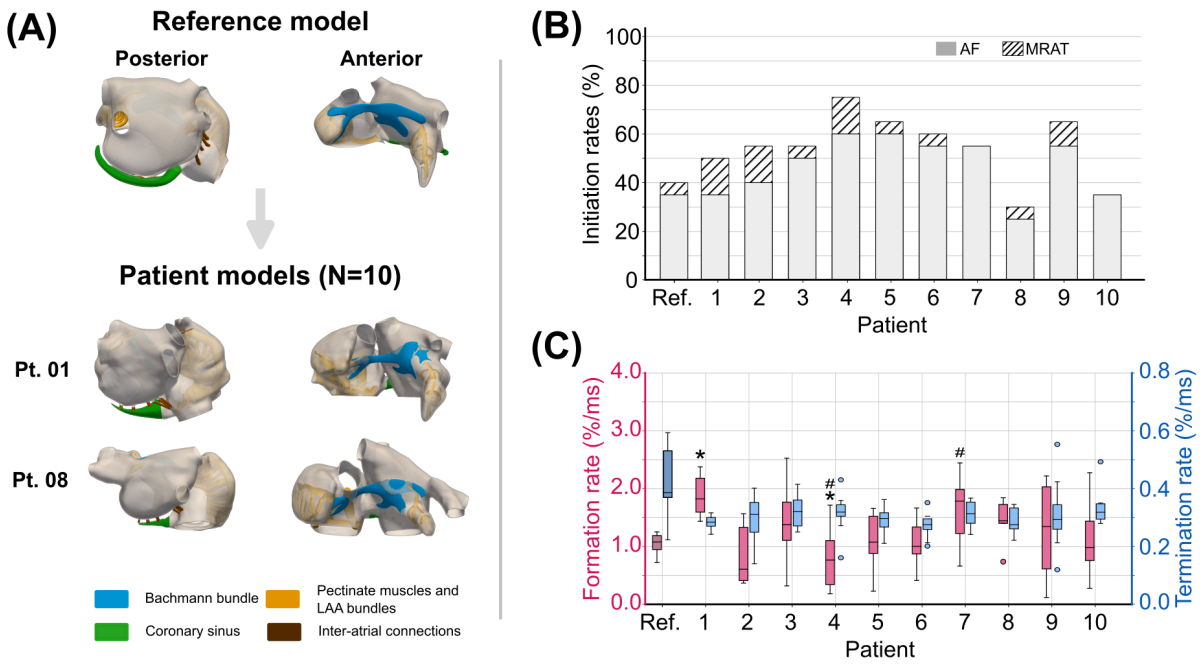

Figure 1. Model examples (A) and variability in AF/MRAT inducibility (B) and AF dynamics (C) between patient models. Reentry formation and destruction rates are shown in magenta and blue, respectively. Pairwise significant differences are indicated with $\star$ and $\#$.

Fig. 1B shows the AF and MRAT initiation rates for the personalized models in comparison with the reference model. The average initiation rates were 50.0% [36.2%; 53.8%] for AF and 55.0% [51.2%; 63.7%] and 57.5% [47.5%; 60.0%] for SVTs. The initiation rates for AF (p=0.432) and SVTs (p=0.142) did not differ significantly among the personalized models.

The AF episodes initiated in each patient model presented different degrees of complexity that depended on the anatomical changes and presence of fibrosis. Fig. 1C displays the reentry inter-formation (λ_f, in magenta) and destruction rates (λ_d, in blue). Significant differences in λ_f show variability in the AF complexity range depending on the patient anatomy, while λ_d was similar across patients. Fig. 2 shows an example of the changes in reentry dynamics for AF episodes initiated from the same pacing location in two different patients. The higher λ_f for the patient displayed in green is reflected by the higher number of reentries (Fig. 2A), resulting in more reentries simultaneously existing at any given time (Fig. 2B).

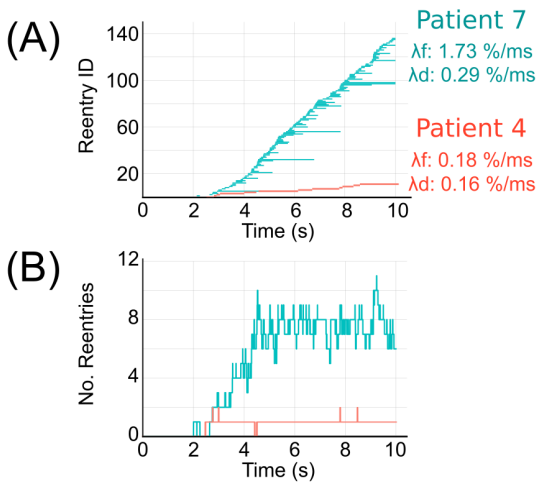

Figure 2. Example of the different AF reentry formation (A) and number of simultaneous reentries (B) in two different patient anatomies.

4. Discussion and Conclusion

We proposed a novel strategy for generating personalized atrial models with variable wall thickness and contact between myocardial layers to investigate the effect of anatomical variability on AF vulnerability and dynamics. Using population-level data to enhance anatomies segmented from LGE-MRI, we incorporated structures not visible in this imaging modality. Our findings show that anatomical variations influenced AF and MRAT initiation rates and significantly affected the complexity of result-

ing AF episodes even in this small cohort. This work advances the development of realistic patient-specific computer models, improving the understanding of how personalized anatomies may impact AF vulnerability and complexity in-silico.

Our model includes pectinate muscles in the RA and LAA with discontinuous contact with the atrial wall, which is critical for AF vulnerability and stability, as transmural breakthroughs often occur during AF [8] and may be associated with micro-reentries involving these structures [9]. Thus, the inclusion of such structures may be crucial for accurately identifying areas in the atria able to maintain reentrant activity in specific patients.

We consider AF inducibility with incremental pacing as indicative of AF vulnerability. Our personalized models showed higher initiation rates than in similar volumetric models [10], suggesting that the unique anatomical characteristics included in those models notably impact the AF vulnerability assessment. However, differences in induction protocols and vulnerability metrics across studies complicate comparisons and warrant further investigations into the model characteristics that most impact inducibility.

Despite identical electrophysiology, AF dynamics varied between patient models, as evidenced by the differences reentry formation and destruction rates. Estimating these rates can be relevant for patient-specific simulations, helping to assess the likelihood of spontaneous termination [11] and develop personalized treatments. Future work should validate whether models replicate patient-specific reentry dynamics and identify which other parameters may need personalization.

Limitations

Our analyses were restricted to a limited set of patients from which only LGE-MRI and limited clinical data were available. Moreover, the model personalization pipeline is based on a single reference model, limiting the variability of the resulting models.

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