Role of Heterogeneous Ionic Profiles in Atrial Fibrillation Propagation. A Population of Models Study

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Abstract

Atrial fibrillation (AF) is characterized by irregular and discontinuous propagation in the atrial muscle. Experimental data show heterogeneity regarding ionic profiles throughout different regions of the atrium. In this study, the effect of the interaction of tissue with different ionic profiles is evaluated in terms of wave propagation.

An experimentally calibrated population of AF profiles was generated. Ionic profiles fitting physiological biomarkers on 1Hz pacing protocols and capable of self-sustaining reentrant activity were evaluated. A bilayer rectangular mesh was simulated including the basal model and one of the population models (N=144). A functional reentry was started on the basal region and the wave propagation to the altered region was classified as Continuous Propagation (CP) or Wave Break (WB).

Results showed 65 CP and 64 WB patterns. Regarding ionic variations, lower I_{K1}, I_{Na} and higher I_{Kur} were associated with WB. Considering biomarkers at 1 Hz, higher Resting Membrane Potentials, longer AP Duration and larger AP Amplitude are associated with WB.

Differences in ionic profiles and AP biomarkers along the tissue result in irregular wavefront propagations. Characterization of ionic profiles can help to better reproduce those conditions observed in clinical and experimental practice.

1. Introduction

Atrial fibrillation (AF) diagnosis is based in ECG registers presenting irregular RR intervals and no discernible repeating P waves [1]. It differs from other atrial tachyarrhythmias, such as atrial tachycardia or atrial flutter, that present high frequency repeating P waves [2].

Only irregular electrical activity in the atrial tissue can present nonrepeating activity in the ECG. High frequency reentrant activity in specific areas of the atrial tissue is said to be responsible for the maintenance of AF. This high frequency activity propagates irregularly to the rest of the atria, leading to turbulent propagations or Wave Breaks (WB) [3]. These irregular propagation patterns result in distinct areas activating at different frequencies, higher frequency regions have been described as those responsible for AF maintenance [4].

Computational models trying to reproduce AF behaviors mainly focus on the location, activation frequency or other relevant parameters associated with functional reentries. However, they present some difficulty when it comes to reproducing irregular behaviors as those present in characteristic AF patterns.

Heterogeneity in terms of ionic currents along the atrial tissue has been described [5]. It results in different Action Potential (AP) curves that interact during AF episodes. Although the experimental data that describe the heterogeneity of ionic profiles along the atria is limited, hence even more in pathological conditions, this study aims to evaluate which ionic profiles have a greater willingness to show in irregular propagations when interacting with tissue that maintain AF rotors.

2. Materials and methods

2.1. Population of models

An experimentally calibrated population of human AF models was generated from the experimental data described in Table 1. The latter describes maximum and minimum values for different AP biomarkers measured at 1 Hz in samples from 149 patients [6,7]. AP biomarkers are represented in Figure 1.a.

Table 1. Experimental biomarkers.

Biomarker	Minimum Value	Maximum Value
APD90 (ms)	140	330
APD50 (ms)	30	180
APD20 (ms)	1	75
APA (mV)	80	130
RMP (mV)	-85	-65
V20 (mV)	-30	20

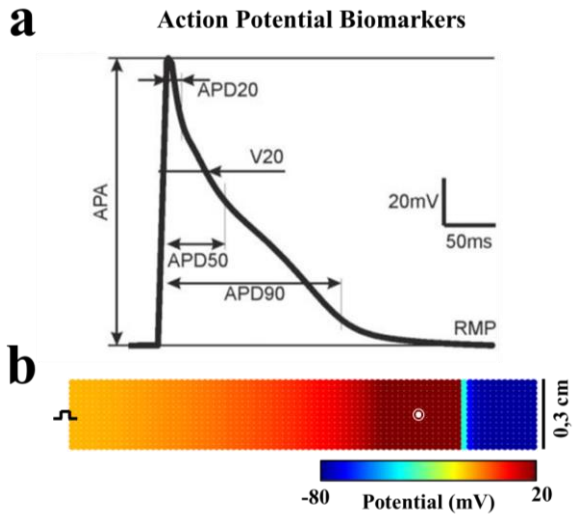

Figure 1. a) Action Potential Biomarkers. AP duration at 20%, 50% and 90% of repolarization (APD20, APD50, APD90, respectively), AP amplitude (APA), resting membrane potential (RMP) and AP potential at 20% of APD90 (V20). b) Geometrical mesh used in the 2104 simulations run to obtain AP biomarkers in the original population. The node evaluated is highlighted in the figure.

A "baseline chronic AF (cAF) model" was used with the following modifications to the Koivumaki et al. [8] model: SERCA expression (-16%), PLB to SERCA ratio (+18%), SLN to SERCA ratio (-40%), maximal I_{NCX} (+50%), sensitivity of RyR to $[Ca^{2+}]$ SR (+100%), conductance of I_{CaL} (-59%), conductance of I_{to} (-44%), conductance of I_{Kur} (-22%) and conductance of I_{K1} (+100%).

The Latin hypercube sampling methodology was applied to the baseline cAF model obtaining an original population of 2104 elements: ionic conductances (g_{Na}, g_{CaL}, I_{NaK}, g_{K1}, g_{to}, g_{Kr}, g_{Ks}, g_{Kur}) took random-sampled values between –75% to 150% of their original value.

Simulations in rectangular bilayer tissues (0.3x2x0.025 cm, inter-node distance 0.25 mm, diffusion 0.24 μm^2/ms, Figure 1.b) were run for each of the 2104 models of the original population. Simulations consisted in a train of 20 stimuli from the narrow side of the rectangle at 1 Hz, biomarkers were analyzed for one point far enough from the borders.

Our population of models was constituted by the 144 models whose biomarker values met the range in Table 1 and maintained a self-sustained functional reentry in a square bilayer tissue of 5 cm on each side (inter-node distance 0.25 mm, diffusion 0.24 μm^2/ms).

2.2. Propagation evaluation in heterogeneous tissues

A bilayer rectangular mesh (5x10x0.025 cm, inter-node distance 0.25 mm, 160.000 nodes, diffusion 0.24 μm^2/ms, Figure 2.a) was simulated including the basal model (left), one of the population models (right) and a transition zone of 1cm.

A functional reentry was started on the basal region by S1-S2 stimulation protocol. Five S1 stimuli from basal model narrow side with period 200 ms were followed by a S2 stimuli at 1155 ms (S= 155 ms), S2 was applied to an area in the top left of the rectangle (Figure 2.a), resulting in a counterclockwise functional reentry.

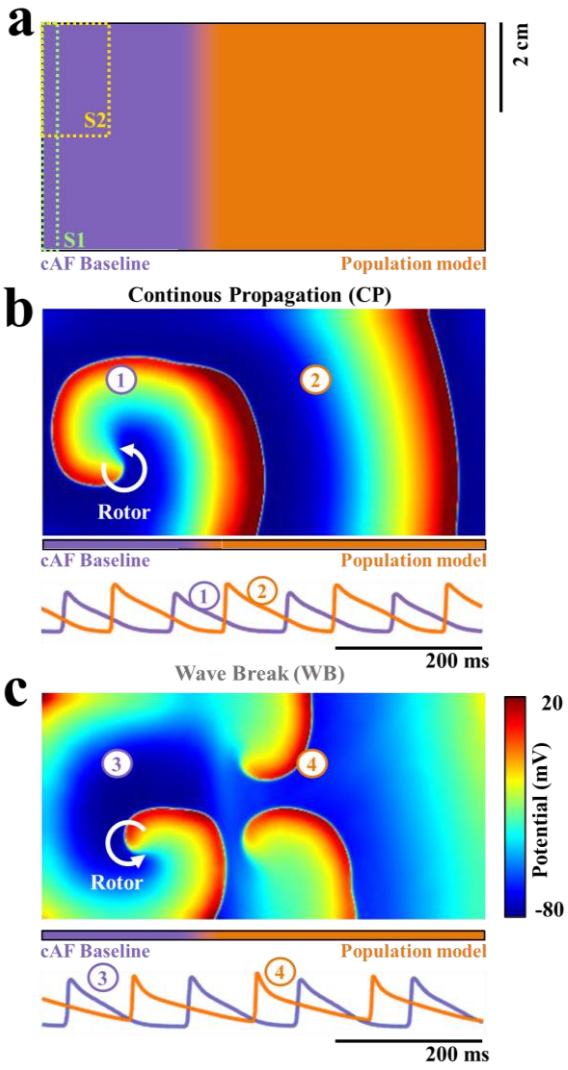

Figure 2. a) Bilayer mesh used for the propagation evaluation in heterogeneous tissues. Colors represent if the nodes correspond to cAF Baseline ionic profile or to one of the 144 models of the population. S1 and S2 areas are highlighted. b) Example of CP: no breaks in the wavefronts can be appreciated and the transmembrane potentials show how the activation frequency in the altered area corresponds to that in the cAF Baseline area. c) Example of WB propagation: a WB can be appreciated, in this case near to the transition zone. Transmembrane potentials present different activation frequencies, not all the activations from the rotor reach the right of the tissue.

Wave propagation to the altered region was classified as Continuous Propagation (CP, Figure 2.b) or Wave Break (WB, Figure 2.c). CP consisted in 1:1 propagation, which means that all the wavefronts coming from the rotor were able to cover the entire rectangle. In contrast, in WB cases some of the reentrant wavefronts presented irregular propagations from left to right.

WB and CP models were compared in terms of ionic profiles and biomarkers. The Mann–Whitney U test, which is robust in nongaussian distributions, was used to evaluate statistical significance ($p<0.01$).

3. Results

3.1. Population of models

Figure 3.a presents two AP for the 2104 models simulated according to section 2.1. The population fitting physiological biomarkers (blue) presented different RMP or APD among other biomarkers.

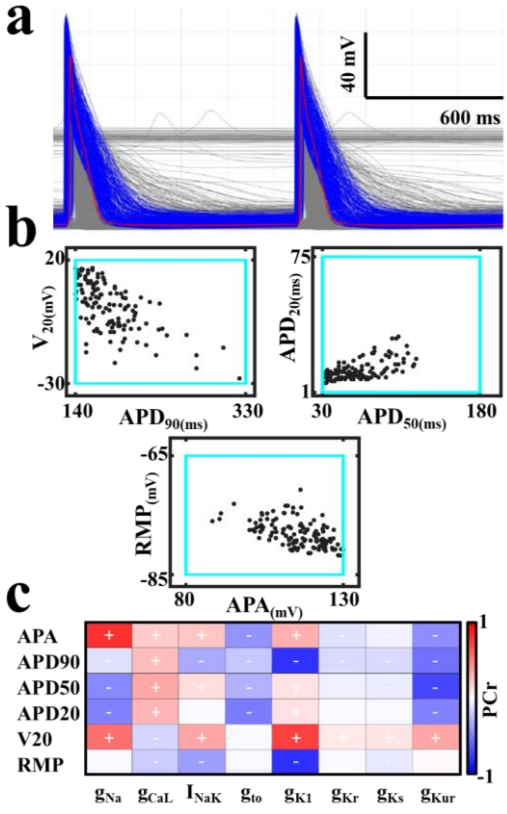

Figure 3. a) APs for the 2104 models of the original population for stimuli 19 and 20. In blue the models of the resulting population of models (N=144) in red the baseline cAF model, in gray discarded models. B) Scattergrams for the biomarkers in the resulting population c) Partial correlation coefficients (PCr) between ionic parameters and AP biomarkers, darker colors represent higher correlations.

The variability of AP biomarkers at 1 Hz is better described in Figure 2.b. The population of models evaluated (N=144) is depicted in three scatterplots combining the six biomarkers. The area resulting from the experimental biomarker values was reasonably covered by the obtained populations of mathematical models and low correlations between biomarkers were observed accordingly to that observed in previous studies [6,7]. Note that models with long APD_{20} and APD_{50} or high RMP could not maintain a self-sustained functional reentry.

The relative effects of ionic parameters in each AP biomarker were analyzed by partial correlation (PCr) on the population of models (Figure 3.c). Direct correlations are marked in red whereas inverse correlations are plotted in blue, the intensity of the color depends on the magnitude of the correlation. This representation allowed to identify those ionic parameters with a lower effect in biomarkers (g_{Kr} and g_{Ks}) which contrast with the rest of the ionic parameters evaluated.

Regarding AP biomarkers, high correlations (g_{Na} *vs* APA; g_{K1} *vs* APD90, RMP and V20 or g_{Kur} *vs* APD50) were observed. However, it was also shown that most AP biomarkers were highly affected by different ionic parameters so, AP curves are highly multiparametric and multiple ionic parameter combinations may result in physiologically feasible models.

3.2. Propagation evaluation in heterogeneous tissues

Examples of Wave Break and Continuous Propagation have been presented in Figure 2. For the population of models evaluated (N=144) the simulations showed 65 CP (black in Figure 4) and 64 WB (gray in Figure 4) patterns. For 15 ionic profiles (red dots in Figure 4) the rotor on the basal region was dragged to the right, ending the reentry.

Figure 4.a describes differences on the ionic current parameters observed between CP and WB models: lower I_{K1} and I_{Na}, and higher I_{Kur} were associated with WB.

Regarding AP biomarkers (Figure 4.b) higher RMP, lower V20, smaller APA, longer APD90 and shorter APD50 resulted in WB propagations.

This was were coherent to the presented in Figure 3.c. Lower I_{K1} results in lower V20, higher RMP and longer APD90; lower I_{Na} results in smaller APA and lower V20 or higher I_{Kur} results in shorter APD50. All the PCr presented before were associated to WB propagation.

4. Conclusion and discussion

In this study, a population of 144 mathematical models representing the variability observed in clinical practice, was used to evaluate the ionic parameters responsible for the WB propagation observed in fibrillatory conditions. The role of I_{Na}, I_{K1} and I_{Kur} stands out from all the others.

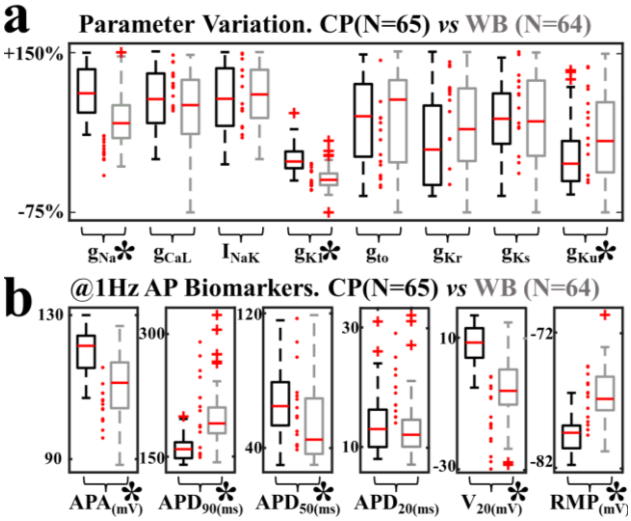

Figure 4. a) Box plots of ionic current parameters in models presenting a Continuous Propagation *(black)* and Wave Break propagation *(gray)*. b) Box plots of AP biomarkers in CP *(black)* and *(gray)*. (* means p<0.01).

No less important are the differences observed in biomarkers. High RMP and small APAs together with long APD90 and short APD50, are representative of WB.

However, it is important to highlight the overlap observed between groups. As other electrophysiological events described by populations of models [6,9], WB propagation is multiparametric, and different ionic profiles, which may not respond to the description presented before, can result in WB propagation.

Simulation studies are commonly associated with *in silico* models configured with a single set of parameters. Those are commonly calculated from multiple experimental results which present variability. Simulations conducted using populations of models allow to better describe the inter-patient variability. This also allows us to emphasize significant trends, as well as to capture individual patterns that may arise in clinical practice.

This study presents different limitations, such as the effect of diffusion and fiber orientation, which were not evaluated. Moreover, the presence of fibrotic tissue has been described as important for wave propagation. In addition, the experimental biomarkers used came from right atrial appendages and may not be representative of the whole atria. Furthermore, we observed the models presenting WB propagation for a single cAF tissue, but it is needed to evaluate what happens if rotor maintenance depends on tissues with different ionic parameters.

Differences in ionic profiles along the atrial tissue may result in WB propagation and thus, in fibrillatory patterns like those observed in the experimental practice. In the development of digital twins, models should account for the different ionic profiles (or AP biomarkers) along the atria to better reproduce fibrillary patterns of each patient.

Acknowledgments

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