Multiple P-wave morphologies in Paroxysmal Atrial Fibrillation patients during Sinus Rhythm: A simulation study

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Abstract

Atrial Fibrillation (AF) is the most common cardiac rhythm disorder worldwide whereas in Paroxysmal AF (PAF) patients, the leading role for its onset is the underlining electrical remodeling. P-wave in electrocardiographic (ECG) signals represents the activation of the atrial substrate. Its shape is influenced by the origin of the sinus rhythm (SR) and the conduction of each part of the atria and thus the analysis of its morphology (PWM) can reveal information related to the atrial conduction routes. Recently, the analysis of the P-waves from ECG signals of PAF patients during SR, revealed the presence of a distinct secondary P-wave morphology in a remarkable percentage of beats, besides the majority of the P-waves matching a main P-wave morphology. We hypothesize that the variability on the PWM can be attributed to the transient modification of the conduction route which is the result of the shift of the pacemaker location within the sinus node (1x1cm). In this study, we incorporated the electrophysiological model of Courtemanche et al. in a 2D tissue describing the left and the right atria, while tissue heterogeneities were also considered. Multiple simulations were conducted, in the normal and electrical remodeled tissue, in each of them the pacemaker location was shifted within the sinus node. The simulation were conducted in CHASTE platform, in order to investigate the conditions under which it is possible to reproduce the different activation pathways in PAF patients while in SR. The initial results are presented here however, the use of a 3D realistic model of human atria is a necessary as a next step to investigate the reproducibility of the results while longer timeframes must be employed in order to reveal the conditions under which the pacemaker location shifts.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and it is associated with increased morbidity and mortality. AF is characterized by an abnormal rapid activation of the aatria resulting in the reduction of contractility in the atrial muscles. In patients with paroxysmal AF (PAF), electrical remodelling is observed, which studied at tissue level. More macroscopically, multiple studies revealed that the analysis of the P-wave characteristics in the surface electrocardiographic (ECG) recordings, during SR can reveal information related to the atrial substrate [1].

According to [2], P-wave morphology depends on (1) the origin of the SR as well as (2) the conduction route. In addition, the variability of the P-wave morphology can be attributed to the transient switch from one group of pacemaking cell to another, within the SA node, or on the different activation routes [3]. The existence of a distinct secondary P-wave morphology in PAF patients was found in [4] while the percentage of beats matching the main or the secondary P-wave morphology can be a predictive metric for the success of PV isolation [5] or for the prediction of AF initiation [6].

In order to understand the underline mechanisms of these phenomenological observations related to arrhythmogenesis, computational modeling constitutes an emerging area of research [7]. Computer simulations have the main advantage that repeated experiments can be performed in a controlled environment while they can shed light on the phenomenological organ level findings such as those detected in electrocardiographic (ECG) recordings and the multiscale mechanisms. In this work, the hypothesis under examination is that the variable location of the pacemaker origin combined with the electrical remodeling, observed in PAF patients, can facilitate the modification of conduction routes leading to the multiple P-wave morphologies. Towards this goal, a simplified 2D atrial geometry, from both atria, was created.
2. Methodology

In this study, both atria were studied using 2D tissue of 5x10cm. The geometric representation of the atria is depicted in Fig1. A number of Pectinate Muscles (PM) were included along the Crista terminalis (CT) as parallel ridges that run on the Right Atrium (RA). The width of the CT were set equal 0.6cm while for the PM the width was found to be close to 0.2cm [8]. The stimulation originated from an area of 1cm² representing the SAN area [9]. Regarding the Left atrium (LA), 2 PVs were included in the model which cover an area of 1cm² [10] and were considered as 0 conductivity. The electrical activation of the LA was considered to happen through the CT.

![Figure 1 Tissue model of both atria (RA: Right Atrium, LA: Left Atrium, CT: Crista Terminalis, PM: Pectinate muscles, PV: Pulmonary Veins)](image1)

Table 1 Ionic properties of different atrial structures (RA and LA is for the left and Right atrium respectively, CT is for the Crista Terminalis and PM for the Pectinate Muscles)

<table>
<thead>
<tr>
<th>Conductance</th>
<th>RA, PM</th>
<th>CT</th>
<th>LA</th>
</tr>
</thead>
<tbody>
<tr>
<td>g_{to}</td>
<td>1.0</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>g_{CaL}</td>
<td>1.0</td>
<td>1.0</td>
<td>0.67</td>
</tr>
<tr>
<td>g_{Kr}</td>
<td>1.0</td>
<td>0.5</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Based on the simulations, the cells in the CT region present a prolonged Action Potential Duration (APD) and an enlarged plateau voltage compared to the physiological atrial tissue. Regarding the PM the APD was similar as the atrial tissue.

Apart from the differences in the conduction values of the different atrial structures, anisotropy was also considered. In this respect, monodomain model of electrical current flow was adopted and differences along the longitudinal and transverse were applied. The ratio of the conductivity along the transversal and longitudinal dimension for the conduction bundles (CT and PM) was set to 1:9 with the longitudinal direction being parallel to the main axis of the bundles. For the rest of the atrial tissue, the conduction was considered to be isotropic. The transversal conductivity was set to 0.15 S/m for both CT and the atrial tissue whereas this value was set equal to 0.11 S/m for PM [8].

The experimental data of ionic channel conductance changes related to PAF have been incorporated in the model of human atrial action potential (AP) developed by CRN in order to obtain the model of PAF atrial cells. Based on [12] the conductance of IK1 was increased by 100% in order to reproduce atrial remodelling under PAF conditions. In the context of the current work, the atrial remodelling was only considered in the RA.

Chaste (Cancer, Heart and Soft Tissue Environment) was used in order to run the simulations described above. Chaste is a general purpose simulation package aimed at multi-scale, computationally demanding problems arising in biology and physiology [13].

3. Results

The stimulation protocol followed included 4 consecutive stimuli at the same areas and a fifth originating either from the same areas or from another within the SAN, far from the first 4 areas. The frequency of the excitation was approximately 60 bpm and the duration of each stimulus was set equal to 2msec.

![Figure 2 Progression of repolarization in the healthy atria the stimulation originated from the left border of the SAN (top) and form the right border (bottom) at time 50msec (a), 100msec (b), 150msec (c), 200msec (d), 250msec (e), 300msec (f), 350msec (g) and 400msec (h) after the stimulation. Red color denotes greater values while the darkest colors represent values close to -80mV.](image2)
As can be observed from Fig. 2 when the stimulation site of the SAN areas was close to the CT, the activation, because of the fast conduction routes spread through the RA and it passed in the LA. However, small changes are detected in the activation time of each part of the atria, suggesting that even if there is a shift of the stimulation site in the SAN area, the depolarization does not differ significantly, but conduction is rather synchronised, and thus the P-waves have the potential to match a main morphology. In more details, in both cases, the activation wave reaches the LA approximately 70msec after the application of the stimulus, whereas the difference in time for the completion of the depolarization of the LA is only 5msec between the two cases.

![Figure 3 Transmembrane voltage in the atria with electrical remodeling.](image)

This work focuses on patterns of electrical activation progression in both atria and presents the initial comparative analysis com results as regards healthy subjects and those with PAF in order to understand the existence of multiple P-wave morphologies in both categories. According to previous studies, P-wave morphology was found to be influenced by the existence of ectopic foci, but this study is the first to investigate the effect of the modification of the conduction routes, and thus the variations of the P-wave morphologies, when a transient shift of the pacemaker activity, within the SAN is present. The analysis was based on simulations performed in a 2D tissue, including the main anatomical structures of the right and left atrium. The simulations were performed in both healthy whereas electrical remodeling, describing the PAF patients, was also considered. In this work, the electrical remodeling was considered only in the RA.

According to the initial results, the variation of the activation origination in a region of 1cm² resulted in small modifications of the activation pattern and thus it confirms the research findings that multiple P-waves may be found in both healthy and PAF conditions. Furthermore, the modifications of the activation patterns are more apparent, in patients with PAF, whereas in healthy subjects the pacemaking shift does not result on remarkable changes of the activation routes. This finding may explain the reason why in PAF patients, a distinct secondary morphology appears whereas the percentage of the P-waves matching this morphology is bigger.

6. Limitations

Apart from the aforementioned analysis; the factors which result in the variations of the pacemaking activity shift, must be studied. In this respect, the effect of the ANS and the Achetylcholine on the frequency of those variations must be considered. In addition, the analysis performed was based on a 2D tissue which represents a realistic atrial geometry, but not fully detailed with the fiber orientation and all the anatomical structures. Further simulations must be performed to confirm the initial finding presented here. Finally, anatomical models of human torso must also be considered to reconstruct the ECG recording and thus correlate the P-wave morphology deflections with the underground electrical activation of the atria.

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References


