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Spontaneous Termination of Atrial Fibrillation: Study of the Effect of Atrial Geometry in a Biophysical Model

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Abstract—**We studied the mechanisms of spontaneous termination of atrial fibrillation in a biophysical model of human atria, during the eight seconds preceding termination. The earliest detectable changes in the cycle length and the number of wavefronts occurred about three seconds prior to termination. We compared the mechanisms involved in the right and left atrium and investigated the effects of atrial geometry on the termination processes. We observed that cycle length started to increase 800 ms earlier in the left atrium than in the right atrium. Similarly, the number of wavefronts decreased even 1800 ms earlier in the left atrium than in the right one. Significantly fewer episodes terminated in the left atrium. Four areas of the atrial geometry showing distinct termination mechanisms were identified.**

I. Introduction

SPONTANEOUS termination of atrial fibrillation (AF) can be observed in clinical studies and computer simulations. So far the mechanisms of this termination are not fully understood. Identification of the spontaneous termination mechanisms could lead to a better understanding of AF and therefore to the development of more effective therapies. However it is difficult to study spontaneous AF termination episodes in detail since they are transient and sometimes very short. Increasing efforts are currently dedicated to the precise analysis of these events.

Clinical studies have been conducted mostly on paroxysmal AF observed from non-invasive 24-h Holter recordings [1,2], from mapping experiments [3] or from data collected in implantable devices [4]. According to these studies, the processes involved in spontaneous AF termination can occur at different time scales. On the one hand, Alcaraz et al. revealed in a study in patients with paroxysmal AF that an atrial organization is detectable in electrocardiographic signals up to one minute prior to termination [2]. On the other hand, a study of 24-h Holter recordings of spontaneous paroxysmal AF terminations by Petrutiu et al. showed that the changes in frequency preceding termination are abrupt and occur only during the last 1-2 s of the episode [1]. Ndrepepa et al. presented a mapping study of spontaneous AF termination using a basket catheter and showed that the earliest detectable event occurred on average 4 s before termination [3]. Furthermore, it was observed that AF termination was polymorphic with heterogeneous groups of unstable rhythms and differences could be observed between the right and left atrium.

The use of a computer model allows the generation of a high number of spontaneously terminated AF episodes in a much easier and spatially more complete way than in clinical settings. Furthermore, all variables of interest are accessible and it is possible to analyze the mechanisms on different temporal and spatial scales compared to what can be achieved during clinical experiments. We previously developed a biophysical model of human atria and studied the role of wavelength during AF, confirming that a critical value was needed to sustain AF when the perpetuation mechanism relied on multiple reentrant wavelets [5].

In the present model-based study, we further analyzed simulated episodes of spontaneous AF termination to assess the temporal and spatial scales of the mechanisms involved and the effect of atrial geometry, specifically the difference between AF dynamics in the right atrium (RA) and left atrium (LA).

II. Methodology

A. Simulation of Atrial Fibrillation

The biophysical model of the human atria has a three dimensional monolayer structure with a realistic size and geometry derived from MRI segmented slice by slice with a 1 mm spacing [6]. After surface smoothing, a triangular mesh of 100'000 nodes (400 μm resolution) was constructed. At each node a modified Courtemanche atrial cellular model was used: the I_{to}, I_{Cal}, and I_{Kur} currents were reduced by 80 %, 30 % and 90 % respectively and the I_{Kr} current was increased by 50% [6,7]. These modifications shortened the action potential duration to 210 ms, while reproducing the restitution properties measured in human atrial cells during chronic AF [8]. The atrial substrate was homogeneous with a conduction velocity of ~40 cm/s.

AF was initiated by decremental ramp pacing at the sino-

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atrial node region, starting at a pacing period of 280 ms, with a 1 ms decrement at each pacing beat. The total duration of ramp pacing was 20 s and AF could be observed after 9 s. We selected as initial conditions 50 instantaneous transmembrane potential maps during the pacing phase: from 9600 ms to 19400 ms after the beginning of pacing, with 200 ms steps. For each of these initial conditions we let the system evolve freely until spontaneous termination. Following this protocol, we could simulate 50 different AF termination episodes.

B. Analysis of the Time Scales of Termination

To assess the time scales involved in the AF termination process, we measured different parameters during the 8 s preceding termination (Fig. 1). We first computed the duration of each AF episode until spontaneous termination. We then computed the temporal evolution of AF cycle length (*AFCL*) as a spatial average of the beat-to-beat intervals measured with 64 electrodes uniformly distributed over the surfaces of both atria (32 on the RA and 32 on the LA).

We characterized the AF dynamics by two parameters: the number of wavelets present in the atria and the number of wavefronts (*#WF*). A wavelet was defined as a spatial zone of neighboring atrial cells with a transmembrane potential higher than -60 mV. Wavefronts were defined as the depolarizing fronts of wavelets, computed as the zones located at the edge of a wavelet with a positive derivative of the transmembrane potential. Therefore, there could be more wavefronts then wavelets.

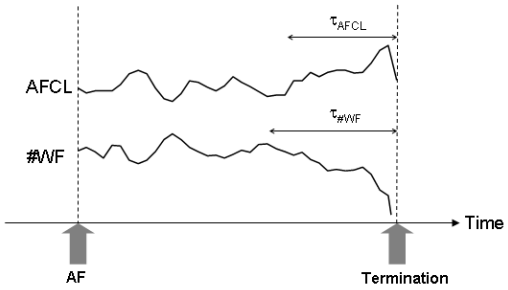

Fig. 1. Analysis of the time scales of termination. *AFCL* represents the spatially averaged AF cycle length and *#WF* the number of wavefronts present in the atria.

We computed τ_{AFCL} and $\tau_{\#WF}$ as the time from the onset of the last *AFCL* increase or the last *#WF* decrease prior to AF termination (Fig. 1). Each measure was systematically computed globally in both atria, and separately in the RA and the LA. The sampling period was 1 ms for *AFCL* and 5ms for *#WF*. A moving average was performed on the *AFCL* and *#WF* with a sliding window of 1000 ms shifted by 100 ms increments.

C. Analysis of the Spatial Localization of Termination

Through visual inspection, we assessed the sites of extinction of the last active reentrant wavefront before AF termination. In most cases, this last wavefront was annihilated by one or several collisions, generating a bigger and more uniform wavefront that died out in one of the extremities of our geometry. Therefore, this was the site where AF terminated but not necessarily where electrical activity was present last in the tissue. We compared the spatial distribution of these AF extinction sites as well as the temporal evolution of *AFCL* and *#WF* for the RA and the LA. Finally, based on the analyses described above, we identified in our atrial geometry regional areas with distinct termination mechanisms.

III. Results

In our simulations, AF was observed as several meandering wavelets (from 1 to 4). The average number of wavelets in the RA was 1.1±0.01. This corresponds to type I and type II AF as described by Konings et al [8]. Mean AF episodes duration was 8.49±7.11 s. However when looking at the histogram of Fig. 2, most episodes terminated in an average time of about 6 s and only four episodes lasted much longer (up to 45 s, Fig. 3).

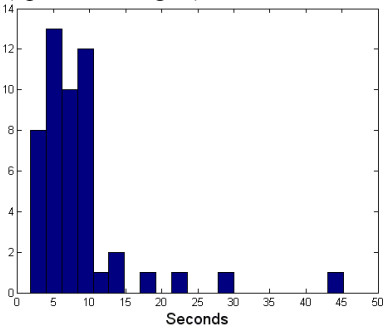

Fig. 2. Histogram of the duration of the 50 AF episodes.

Fig. 3 represents the spatial localization of the AF extinction sites for both atria. Significantly fewer episodes ($p<0.001$) terminated in the LA (9/50) compared to the RA (41/50).

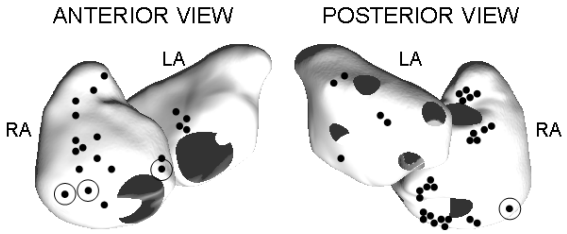

Fig. 3. The atrial anatomy with the AF extinction sites (represented as black dots) for the 50 simulated AF episodes. The four encircled sites represent the episodes with AF duration longer than 15 s.

Fig. 4 shows the temporal evolution of *AFCL* and *#WF* averaged on the 50 AF termination episodes, computed either globally for both atria, or separately in the RA and the LA. *AFCL* started to increase about 3 s before termination on a global scale, but 800 ms earlier in the LA (τ_{AFCL}=3200 ms) than in the RA (τ_{AFCL}=2400 ms). In a similar way, *#WF* started to decrease 1800 ms earlier in the

LA ($\tau_{\#WF}$=3000 ms) than in the RA ($\tau_{\#WF}$=1200 ms). Therefore, an asymmetry in dynamics between atria could be observed even in the presence of a homogeneous substrate. These results are in agreement with the clinical observations on humans from Ndrepepa et al., where the earliest detectable event occurred on average 4 s before termination with a significant increase of cycle length in the LA first, followed by an increase in the RA only 1 s later [3].

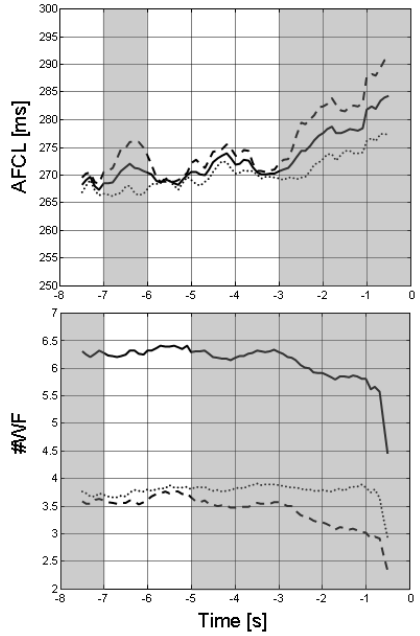

Fig. 4. Mean temporal evolution of *AFCL* and *#WF* in both atria (solid line), in the RA alone (dotted line) and in the LA alone (dashed line). Instants when a significant difference ($p<0.001$) could be observed between the RA and the LA are highlighted in grey.

Although the averaged curves of Fig. 4 provide valuable information about the general dynamics of termination, we noticed that major differences in dynamical features could be observed from one episode to another. Motivated by this finding, a detailed analysis of the spatial distribution of the AF extinction sites, as well as the reentry patterns just before termination, was conducted for each episode. As a result, we were able to define four groups of episodes, each one corresponding to a specific location of the AF extinction sites (Fig. 5): left atrium (LA, 9 episodes), right atrial free wall (RAW, 14 episodes), inferior vena cava (IVC, 10 episodes) and superior vena cava (SVC, 14 episodes).

The mechanisms of termination in these four groups were the following: two waves could either collide and, hence, annihilate each other or a wave could hit a refractory zone. Interestingly, for each of the three groups in the RA, a similar termination pattern involving the annihilation of the last wavefront by a refractory block could be observed (Fig. 6). In contrast, no systematic termination pattern could be observed in the LA group.

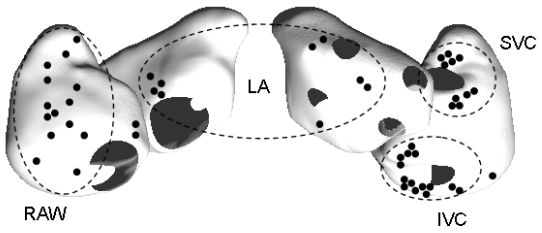

Fig. 5 Definition of the four groups based on the AF extinction sites.

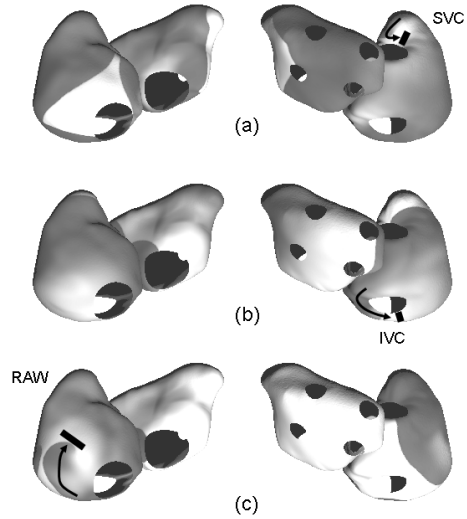

Fig. 6. AF termination through annihilation of the last active reentrant wavefront (indicated by the arrows) by a propagation block created by refractory tissue (thick black lines) for the three groups in the RA: (a) SVC, (b) IVC, (c) RAW.

Fig. 7 shows the temporal evolution of *AFCL* resulting from the separate analysis of the termination episodes in the four groups defined in Fig. 5. The results confirm that, although there is an increase of *AFCL* a few seconds before termination in all groups, the individual curves differ both in their temporal evolution and in the differences observed between the RA and the LA. For instance, for the episodes in the IVC group, we observed the formation of a flutter-like activity around IVC 2-3 s before termination (8/14 episodes clockwise and 6/14 episodes counter-clockwise). Then, less than 1 s before termination, this macro-reentrant wavefront was blocked by refractory tissue. This phenomenon is visible in Fig. 7 where *AFCL* increases about 3 s before termination and then remains stable during the flutter-like activity, until a sudden drop in *AFCL* just before termination. In the RAW group, termination was less organized and *AFCL* increased abruptly only in the last second. It is also interesting to note that for the SVC group, no significant difference in *AFCL* was found between the RA and the LA.

Similarly, Fig. 8 shows the temporal evolution of *#WF* for the four groups. Instants when a significant difference between the RA and the LA was observed (highlighted in grey in Figs. 7 and 8) were more frequent for *#WF* than for *AFCL* across all groups, with a significantly higher number of wavefronts in the RA. *#WF* tended to decrease earlier and more gradually for the LA group compared to the groups

located in the RA, which is consistent with the observation made on the measure including all episodes (Fig. 4). In the IVC and SVC groups, there was a two-stage reduction of *#WF*: the first one 3 s before termination and the second one 1 s before. In the case of IVC this corresponds to the creation of the flutter-like activity 3 s before termination, followed by an abrupt propagation block of the flutter wave.

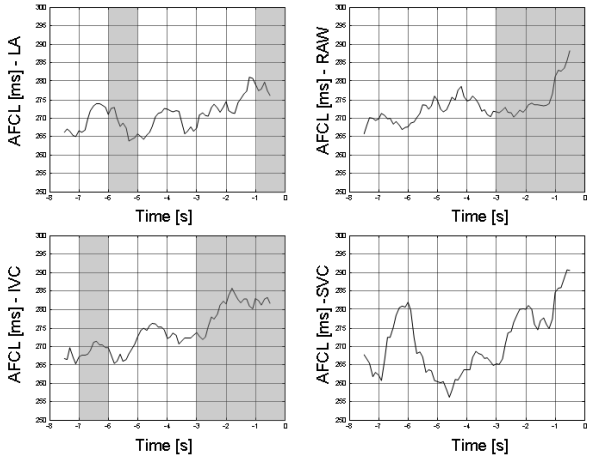

Fig. 7. Mean temporal evolution of *AFCL* computed on the AF termination episodes in each of the four groups LA, RAW, IVC and SVC. Instants when a significant difference ($p<0.001$) could be observed between activity in the RA and the LA are highlighted in grey.

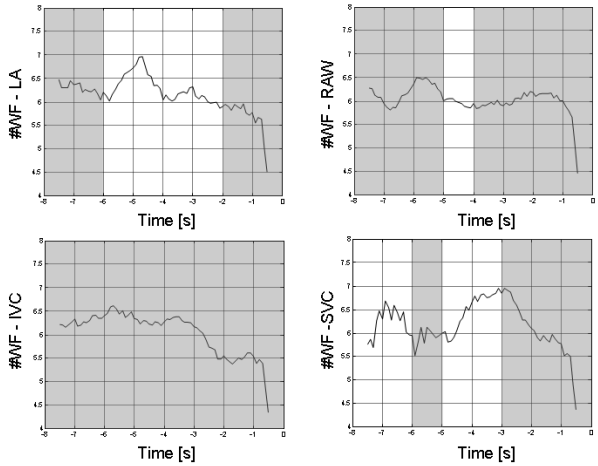

Fig. 8. Mean temporal evolution of *#WF* computed on the AF termination episodes in each of the four groups LA, RAW, IVC and SVC. Instants when a significant difference ($p<0.001$) could be observed between activity in the RA and the LA are highlighted in grey.

These observations highlight the fact that even if the global results shown in Fig. 4 are in agreement with clinical data [3], when looking closer at specific anatomical areas it is possible to observe very different dynamical processes, although the mechanisms triggering these differences are not yet understood. The suspected role of atrial geometry still needs to be further analyzed. Nevertheless, these detailed and systematic observations cannot be easily performed in clinical studies based on surface electrocardiograms or mapping data with a limited number of electrodes.

Our biophysical model has several limitations: in reality paroxysmal AF lasts for several hours (but no more than 2 days), while in our simulations, induced AF terminated spontaneously within a few seconds. Furthermore, the conduction velocity of our model is below values reported in electrophysiological studies, and several anatomical details such as pectinate muscles or crista terminalis were not added to our monolayer geometry. In spite of this, the observed mechanisms of termination seem to be consistent with what has been reported in the literature. The biophysical model represents an efficient tool to complement clinical studies and permits a detailed interpretation of the mechanisms of spontaneous termination.

IV. Conclusion

In a biophysical model of AF with uniform propagation properties we could observe significant differences in the AF dynamics related to the atrial geometry a few seconds before termination. Future investigations will be devoted to the precise description of these mechanisms in terms of dynamical properties, timings and spatial patterns.

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