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Modeling Atrial Pacing*

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Abstract— **We present a model-based study of a therapeutical approach to atrial fibrillation based on pacing. After a systematic evaluation of different atrial pacing sites, we selected pacing from the septum area and designed a novel septum pacing protocol for atrial fibrillation termination. We then evaluated the performance of septum pacing in different models of atrial fibrillation and investigated the effect atrial substrate (cellular properties, anisotropy and heterogeneities) on the ability to capture during pacing. This study highlights the need for the development of patient-specific algorithms for atrial therapies.**

I. Introduction

Atrial fibrillation (AF) is the most common form of sustained cardiac arrhythmia. Its polymorphic dynamical nature prevents the development of a single therapy effective in all individual patients [1]. Several guidelines have been proposed for the management of AF in a clinical settings. For paroxysmal and persistent AF, ventricular rate control and/or rhythm control strategies are proposed, while for patients with permanent AF the objective is sinus rhythm restoration. Pharmacological therapy with antiarrhythmic drugs altering cardiac electrical properties is an important part for any rhythm control strategy and often the first line approach. However due to the side effects of drugs there has been a shift in the last 15 years towards non-pharmacological therapies, including controlled destruction of arrhythmia-generating triggers or atrial tissue (ablation therapy), or implantable devices that can terminate arrhythmia with controlled electrical discharges. Restoration of sinus rhythm is also often achieved by external electrical cardioversion under general anesthesia, a difficult task being the maintenance of sinus rhythm after successful cardioversion. Some of the recent pacemakers and defibrillators have incorporated different features to prevent or terminate AF via pacing. Pacing algorithms designed to terminate atrial tachycardias deliver pacing bursts at a cycle length shorter than that of the detected arrhythmia then gradually decrease the pacing rate. As compared to electrical cardioversion, pacing has the advantage of being painless, safe and energy efficient. However, while the possibility of local atrial capture by rapid pacing has been demonstrated in animal or humans [2,3], no pacing therapy has proved so far to be effective in terminating AF and no clinical study has yet proven the long-term clinical benefit.

Computer modeling has gained increased importance in the development of therapeutical strategies for atrial fibrillation, overcoming some of the limitations encountered in experimental and clinical research. Computer models should aim at accurately reproducing the different AF types in humans creating a basis for substrate-related diagnosis and therapy. The work presented here focused on how pacing could possibly terminate AF.

II. Methodology

A. Biophysical Model of Atrial Fibrillation

The geometry of the biophysical model of the human atria was reconstructed from computed tomography (CT) scans of a patient in AF before an ablation procedure. This resulted in a monolayer tissue embedded in a 3D structure (Fig. 1). After surface smoothing, a triangular mesh of 117'000 nodes (450 μm resolution) was constructed and formed the basis for the application of numerical methods to solve the monodomain propagation equations [4]. The fast conducting Bachmann's Bundle (BB) was included in a similar was as in the Harrild-Henriquez model [5]. Rule-based fiber orientation was also included (Fig. 2) [6,7]. A thick-walled variant of this geometry was also constructed, but at the expenses of an increased computational load [8]. It was therefore not used in the present study.

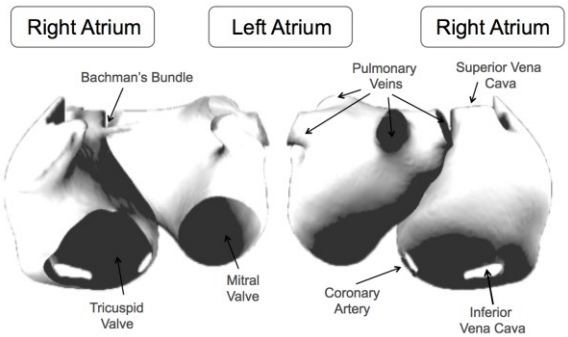

Figure 1. Geometry of the monolayer biophysical model of huma atria. The orifices of the major vessels and valves are represented on the geometry, as well as the fast conducting BB.

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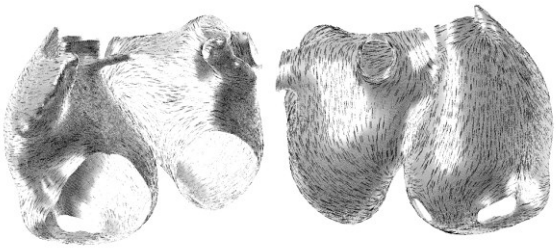

Figure 2. Inclusion of rule-based fiber orientation

B. *Modeling Different Types of Atrial Fibrillation*

A dynamical activation model, based on membrane ion kinetics was assigned to each atrial unit of the grid. Two different cellular models were implemented: 1) a variant of the Luo-Rudy (LR) ventricular model adapted to atrial cellular properties [9,10], 2) a dedicated atrial cellular model, the Courtemanche-Ramirez-Nattel model (CRN) [11]. The CRN model has become popular for the simulation of arrhythmias because quantitative data are available to include the effect of regional heterogeneities, AF-induced electrical remodeling or vagal stimulation through acetylcholine. This CRN model however has a much higher computational load than the modified LR model. In the simplest version of the biophysical model, all cells were assigned homogeneous intrinsic properties using the modified LR model.

Atrial fibrillation was initiated in the biophysical model in a similar way as in clinical experiments, using a programmed stimulation protocol or a burst pacing protocol. Most attempts to initiate arrhythmias in a healthy substrate either failed or produced unstable reentrant waves that terminated after a few seconds. Conditions favorable for the perpetuation of AF were created in models of pathological atrial tissue. While using the same atrial geometry of Fig. 1, different types of sustained AF dynamics could be obtained by varying the cellular properties as summarized in Table I. These models correspond experimentally to different pathophysiologies proposed as being the cause for AF in the human heart.

TABLE I. DIFFERENT AF MODELS

AF Model	Cellular Model	Heterogeneities	Anisotropy
Multiple wavelets	LR for AF Remodeling	Homogeneous	1:1
Cholinergic AF	CRN for AF	Heterogeneities in acetylcholine	3:1
Heterogeneous AF	CRN for AF	Heterogeneities in repolarization	4:1

AF based on multiple wavelets. This model was based on a homogenous and isotropic tissue in which the LR model was adjusted to mimic electrical remodeling as observed in patients suffering from permanent AF, such as shortening of the action potential duration [12]. This was simulated by setting the channel conductance G_{Na}, G_K and G_{si} to 16, 0.423 and 0.55 ms/cm2 respectively. The resulting AF dynamics revealed multiple wavelets continuously changing in size and duration due to functional or anatomical reentries.

Cholinergic AF. This model was based on an atrial tissue with a 3:1 anisotropy and the CRN model for AF [11] in which I_{CaL} was reduced by 70% and I_{to} and I_{Kur} by 50%. An acetylcholine-dependent K+ current I_{KACh} was added [13]. Spatial variations in acetylcholine concentrations were introduced: I_{KACh} was globally increased by 250% while it was decreased by 30% inside the areas of patchy heterogeneities shown on Fig. 3. The resulting AF dynamics was maintained by stable rotors.

AF due to heterogeneities in repolarization. This model was based on an atrial tissue with a 4:1 anisotropy and the CRN model for AF [11] in which the current I_{CaL} was reduced 30%, I_{to} by 80%, I_{Kur} by 90% and I_{Kr} increased by 50% [14]. In addition patchy heterogeneities (Fig. 3) were introduced, in which I_{CaL} was decreased by 50% and I_{to} and I_{Kr} were increased by 300% relative to the original model. Wavebreaks were created by the repolarization gradients and this contributed to the maintenance of AF.

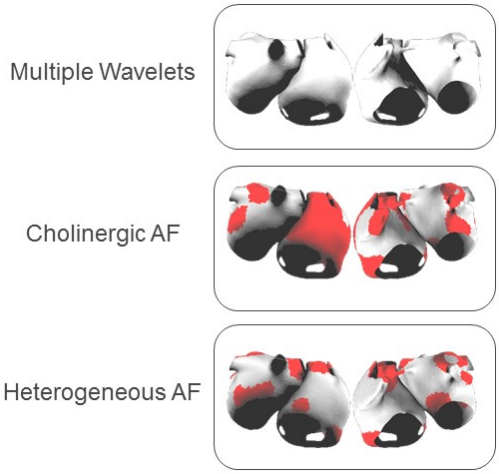

Figure 3. Atrial substrates for the different AF model. The dark areas indicate where the patchy heterogeneities were added.

C. *Modeling Pacing of Atrial Fibrillation*

To perform computer simulations of AF therapies equivalent to animal or clinical experiments, multiple transmembrane potentials (N=16 for the study presented here) were selected during one simulation of sustained AF in each of the AF model. These maps correspond to different states of electrical activity in the atrial tissue. They served as initial conditions for the repetitive application of the pacing therapy. Pacing was simulated by injecting a stimulus current inside the cells located at the pacing site.

Following this scheme, computer modeling permitted a systematic study of pacing algorithms currently used in pacemakers and allowed the search for the optimal pacing sites and pacing cycle length leading to a local capture of AF [15]. As a result a higher ability to sustain capture was found in the right atrial free wall, the left atrial appendage, and the pulmonary veins where the wavefronts induced by

pacing encompassed the major part of the paced atrium. This capture was accompanied by residual reentrant waves outside the area of capture and AF termination was not possible since with a stop of the pacing protocol re-initiation of AF was the rule. When pacing only one atrium, control of both atria was not observed. Obtaining capture in both atria was found possible only when pacing in the septum, although the ability to sustain capture was low. These results therefore confirmed that single site rapid pacing of AF cannot terminate acute nor permanent AF in animals or humans [2,3].

Based on these observations, a novel septum pacing scheme was developed [16]. Pacing was applied from the whole septal area (Fig. 4) according to a dual-stage pacing scheme: rapid pacing during 10-30 seconds at a pacing cycle length (PCL) of 62-70% of the AF cycle length (AFCL) followed by a single stimulus at 130% AFCL and a slow pacing phase during 1.5 seconds at 180% AFCL. This new septal pacing scheme could suppress AF reentries in a more robust was than classical single site pacing, leading to up to 29% of AF termination in computer simulations [16]. Experimental studies are still needed to determine whether similar termination mechanisms and rates would be observed in animals and humans, and in which types of AF this pacing strategy might be the most effective.

In the study presented here, we assessed the impact of the different atrial substrates presented in Table I on the ability the induce capture during pacing from the septum as described in [16]. Rapid pacing was applied from the septum area (Fig. 4) during 30 seconds at PCLs in the range 50-100% AFCL. In this study, we did not take into account activity originating from the sino-atrial node during or after pacing. The septal area in our model consists of normally conducting tissue connected to both atria, with a hole in the middle representing the fossa ovalis.

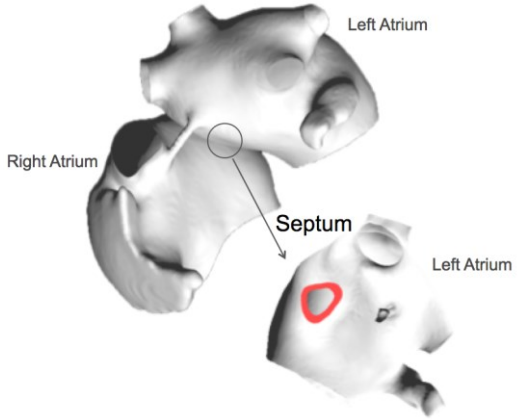

Figure 4. Pacing from the septum area (view of a cut of the left atrium). The shaded area represent the area that is paced during septal pacing.

D. *Assessment of Atrial Fibrillation Capture*

Capture was defined as the ability of the pacing burst to take control over an given area away from the pacing site. It relates to the capture around the pacing site, not to the generalized capture of both atria. During rapid pacing, a set of 24 pairs of electrodes evenly distributed on the atrial surface (Fig. 5) were analyzed in order to determine the percentage of captured atrial tissue. At each pair of electrodes the cycle length and of the direction of propagating waves were assessed: we considered a pair was captured if the direction of propagation was from the interatrial junction to the appendages (as indicated by the arrows in Fig. 5) and the cycle length was equal to the PCL ± 2%. For each pacing sequence, a period of 30 seconds was analyzed and the percentage of capture atrial tissue was computed as the ratio of the pairs where capture was observed divided by the total number of pairs.

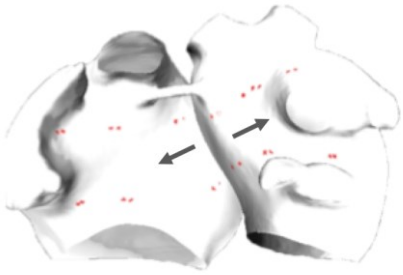

Figure 5. Automatic assessement of AF capture. A set of 24 pairs of electrodes was evenly distributed on the atrial surface in order to assess the cycle length and the direction of propagation of wavefronts.

III. Results

A summary of the capture results obtained for the three AF models is presented in Fig. 6. As expected, the highest capture (80% of atrial tissue) was achieved in the first homogeneous and isotropic model (AFCL=72ms). The capture window was narrow (85-95% AFCL). The model of cholinergic AF showed a broader capture window (65-100% AFCL) but with only about 50% of captured tissue. In the third model based on heterogeneities in repolarization, even if AF was slower (AFCL=220ms) the maximum capture observed was only 30%.

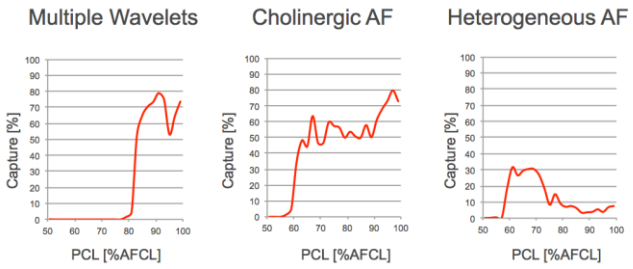

Figure 6. Capture results for the three different models of AF. Percentage of captured atrial tissue represented as a function of the PCL.

The impact of heterogeneities on the propagation of pacing-induced wavefronts and on AF capture was clearly visible in the simulations as shown on Fig. 7. These examples show for each AF model the best capture than can be achieved via septum pacing. The first model based on multiple wavelets is similar to the one we used in the development of the septum pacing algorithm with an AF termination rate of up to 29% [16]. In this case, we could observe a gradual capture of both atria due to the strategic

anatomical location of the septal area. Like in previous experiments, we could observe the presence of residual reentrant wavelets away from the pacing site even during optimal capture, generally anchored around anatomical obstacles [16]. It has been show in [16] that the AF termination rate obtained with the dual-stage septal pacing scheme was proportional to the residual number of anchored wavefronts at the end of the rapid pacing phase. In this model we can also observe that the BB plays an important role on the capture patterns obtained with rapid pacing by rapidly conducting electrical activity between both atria.

In the model of cholinergic AF, the capture patterns were very different and tended to be more regular than with the first model. Most residual reentrant waves were located in the left and right appendages. The BB didn't seem to play an important role and there were less anchored wavelets than in the first model.

In the model of AF based on heterogeneities in repolarization, capture patterns were significantly impacted by the areas of heterogeneities creating wave anchoring and wavebreaks even in areas close to the pacing site. More work is required to assess the impact of such heterogeneities on AF termination rate.

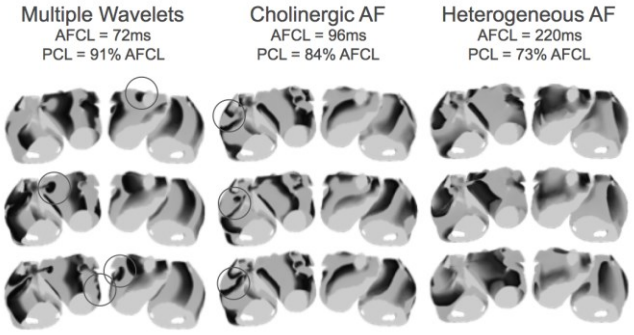

Figure 7. Examples of instaneous transmembrane potential maps during rapid pacing of AF in the 3 different AF models. Light gray represents the resting potential and dark grey the depolarization potential. Residual reentrant wavelets are highlighted with circles.

It has to be recognized that computer models cannot go beyond the information that is integrated in them and that they all have limitations. This model was based on a monolayer three-dimensional surface and did not take into account the impact of thickness of the atrial tissue on the results. Furthermore, it did not take into account anatomical details such as pectinate muscles, the crista terminalis or the coronary sinus pathway. These simplifications are part of a tradeoff between model accuracy and computational load needed to perform large scale simulations. This model studied different atrial substrates without the inclusion of external triggers such as rapid foci originating from the pulmonary veins. Further studies would be needed to address this type of focal AF.

IV. Conclusion

This study showed that heterogeneities in atrial substrate not only play a role in AF perpetuation but also greatly influence the ability to capture AF with rapid pacing. Changes in AF substrates have a significant impact on rapid pacing outcomes, implying that patients may respond in different manners to rapid pacing of AF. This suggests that AF pacing therapies should be dependent on each patient's atrial substrate. The ultimate goal is to use patient-specific computer models based on each patient's anatomy and substrate in order to test an AF therapy in the model before applying it to the patient [8].

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