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Optimization of Antitachycardia Pacing Protocols Applied to Atrial Fibrillation: Insights from a Biophysical Model

Laurent Uldry, Nathalie Virag, Lukas Kappenberger, Jean-Marc Vesin

Abstract—**We present a model-based systematic study of antitachycardia pacing protocols applied to atrial fibrillation, focusing on the ability to achieve and maintain capture during pacing, as a function of both pacing site and period. We observed that pacing sites located away from anatomical obstacles led to faster and more robust capture. Moreover, after comparing burst and ramp pacing, our results indicate that in order to get capture it is necessary to pace at a fixed optimal period over a sufficient long time.**

I. Introduction

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia. Consequences for patients are discomfort, blood clot formation and high risk of embolic stroke. Several treatments are available for restoring sinus rhythm: medication, electrical cardioversion, surgical or catheter ablation and antitachycardia pacing (ATP).

The work presented here focuses on how pacing can control and possibly terminate AF. ATP is used clinically to terminate atrioventricular reentry tachycardias or atrial flutter. In contrast, the effectiveness of ATP applied to patients in AF is not clear even if application in patients has been reported [1]. Mitchell et al. showed that ATP (50 Hz burst pacing during 2 s) is ineffective at terminating persistent AF in humans [2]. On the other hand, the possibility of local atrial capture has been shown in animal and human experiments. In electrically induced AF in dogs Allessie et al. showed that it is possible to capture a small region of atrial tissue of about 6 cm diameter by rapid pacing [3]. However, the resulting paced AF was faster than the original AF and did not lead to termination. Daoud et al. performed pacing in the human right atrium during electrically induced AF [4]. Pacing with a cycle length (CL) 10-50 ms less than the AF CL led to local capture and distant effect in the left atrium but no termination. Pandozi et al. assessed the possibility of local capture in the right atrium in patients with spontaneous chronic AF (pacing at 250 ms CL, decreased by 10 ms every 10 s until a CL of 100 ms) [5]. Local capture was obtained in 87.2 % of pacing sites, with a preference for the right lateral wall over the atrial roof or septum.

In our study we used a biophysical model of the geometry of the human atria derived from magnetic resonance images (MRI) and a model of atrial membrane kinetics [6]. This model has the property of combining complete and realistic atrial anatomy and electrophysiology. Its computational demand permits the simulation of atrial arrhythmias for several seconds or minutes. In previous studies it allowed us to evaluate the effectiveness of different surgical or catheter ablation patterns and to compare simulations results with clinical data [7,8]. We implemented and tested two of the major ATP algorithms currently used in pacemakers, burst and ramp pacing, and determined the optimal pacing sites and pacing periods leading to a local capture of AF.

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 [6-8]. After surface smoothing, a triangular mesh of 50'000 nodes (600 μm resolution) was constructed. At each node of the mesh, the electrical activity was modeled by the Luo-Rudy membrane model adapted to the properties of electrically remodeled atrial cells [9,10].

AF was initiated by 20 Hz pacing during 3 s in the sino-atrial node region (Fig. 1). During this phase, wavebreaks were observed that gradually led to AF. When pacing was stopped, AF was sustained. Subsequently, ATP was tested following a similar methology as used in our previous studies on AF ablation [7,8]. Because of the evolving nature of AF, several moments in AF (three for this study) were randomly chosen for starting the ATP protocols (Fig. 1). These moments correspond to different states of the activity present in the tissue, such as the number of wavelets and their spatial distribution. For each pacing protocol tested, the results presented document the average values observed following these three initial AF conditions.

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L. Uldry is with the Signal Processing Laboratory of the Swiss Federal Institute of Technology, 1015 Lausanne, Switzerland (phone: +41 21 693 56 58; fax: +41 21 693 76 00; e-mail: laurent.uldry@epfl.ch).

N. Virag is with Medtronic Europe, 1131 Tolochenaz, Switzerland (e-mail: nathalie.virag@medtronic.com).

L. Kappenberger is emeritus with the University Hospital CHUV, 1011 Lausanne, Switzerland (e-mail: lukas.kappenberger@chuv.ch).

J.-M. Vesin is with the Signal Processing Laboratory of the Swiss Federal Institute of Technology, 1015 Lausanne, Switzerland (e-mail: jean-marc.vesin@epfl.ch).

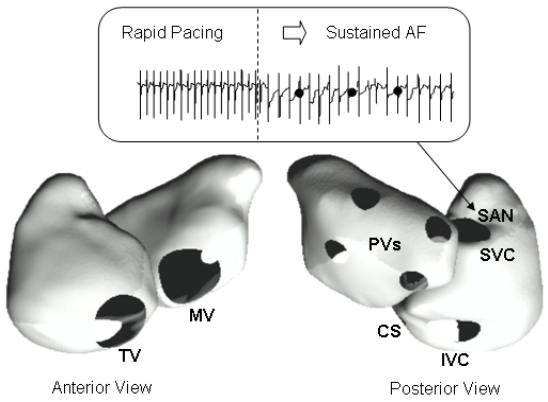

Fig. 1. Generation of the initial AF conditions for the application of the ATP protocol. AF was first initiated by rapid pacing at the sino-atrial node (SAN) region at 20 Hz during 3 s. When pacing was stopped, sustained AF was observed and three initial AF conditions (marked by black dots on the electrogram) were recorded, 30 s, 150 s and 270 s respectively after the end of rapid pacing. The orifices of the major vessels and valves are represented on the atrial geometry: tricuspid valve (TV), mitral valve (MV), inferior vena cava (IVC), superior vena cava (SVC), pulmonary veins (PV) and coronary sinus (CS).

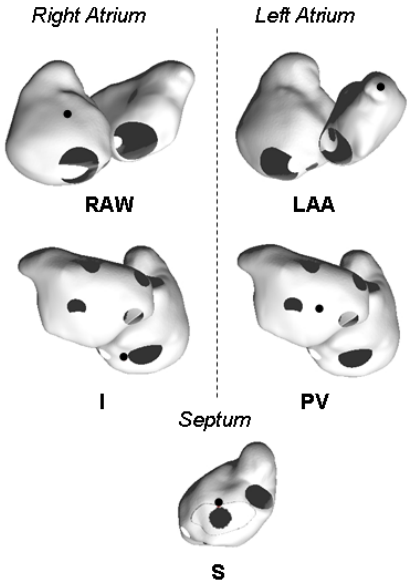

Fig 2. The five different pacing sites tested (black dots): right atrium free wall (RAW), left atrium appendage (LAA), isthmus between inferior vena cava and tricuspid valve (I), pulmonary veins (PV) and septum (S).

B. *Pacing Protocols*

Two types of ATP protocols were compared: burst pacing at constant CL and ramp pacing incrementing CL at each pacing beat. Pacing periods (*PP*) were based on the AF cycle length (*AFCL*), computed as the mean of the 200 interbeat intervals preceding the onset of pacing, at each pacing location. For burst pacing, we tested *PP*s in the range 20-110 % *AFCL* with 5 % increments.

For ramp pacing, we applied a two-stage protocol: 1) incremental ramp pacing during 1.5 s, during which the *PP* was incremented by 1ms at each subsequent beat, 2) burst pacing with *PP* values in the range 20-110 % *AFCL*. The objective of this second protocol was to assess whether a faster capture could be obtained with a ramp preceding the subsequent pacing at a fixed period.

The total duration of both the burst and ramp pacing protocols was 30 s. This duration was chosen based on preliminary observations, indicating that AF capture could be achieved optimally when using this time window.

C. *Pacing Sites*

The pacing sites at which the ATP protocols were evaluated are illustrated in Fig. 2. It includes two sites in the right atrium (RA), two sites in the left atrium (LA) and one on the septum between both atria. For each atrium, we chose one site located away from anatomical obstacles (RAW in RA and LAA in LA) and one site close to major vessels (I in RA and PV in LA).

D. *Capture of Atrial Fibrillation*

Capture was defined as the ability of the pacing burst to take control over an area with a radius greater than 2 cm around the pacing site for a minimum of five consecutive beats. This definition is in agreement with the one used in human experiments [5]. It relates to local capture around the pacing site, not to the generalized capture of both atria.

Capture was assessed as illustrated in Fig. 3. *AFCL* was measured at four sites located ~2 cm distance from the pacing site. For each site, *AFCL* was considered as entrained by the applied rapid pacing if during five consecutive beats the observed *AFCL* was within the range: *PP* ± 3 ms. Capture was taken as achieved if three of the four sites were entrained.

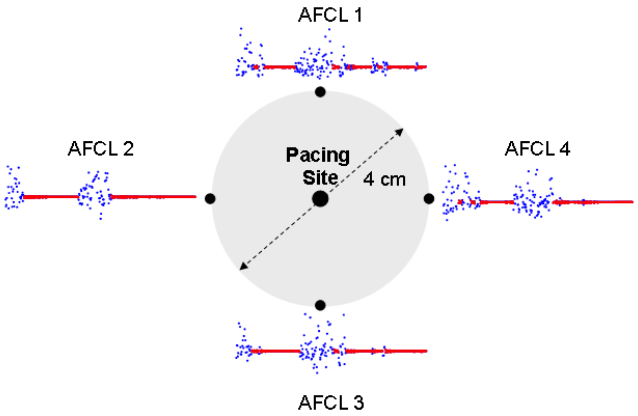

Fig. 3. Defining AF capture: *AFCL* was computed at four locations around the pacing site. When a site was entrained by the rapid pacing, *AFCL* was within the range *PP*± 3 ms. When three out of the four sites were entrained capture was assumed.

For each of the simulations performed, three different measures were used for the documentation of the results.

The first is the interval of *PP* values for which capture was observed during more than 50% of the time, referred to as the Capture Interval. Within the Capture Interval, Time to Capture was defined as the duration from the start of the ATP pacing to the onset of the first capture episode. This parameter provides information on the transient phase between AF and capture, therefore about how easily capture can be achieved. In a similar way, Capture Robustness was defined as the percentage of time spent in capture, starting from the first capture episode until the end of the pacing protocol. It conveys information about how capture can be sustained once it is achieved.

III. Results

The capture results for the different pacing sites and the burst pacing protocol are listed in Table 1. No difference was observed between the Capture Interval values at the different pacing sites if computed as a percentage of *AFCL*, except for I where a very narrow Capture Interval was observed. However, due to the fact that a longer *AFCL* was measured in the septum area, the *PP* computed in ms was significantly longer in the septum than in the RAW ($p=0.012$), the LAA ($p=0.034$) and the PV ($p=0.034$). Therefore, the Capture Interval should be expressed in percentage of *AFCL* in order to be independent of the pacing site.

TABLE I
CAPTURE RESULTS FOR THE DIFFERENT PACING SITES

Pacing Site	Capture Interval	Time to Capture	Capture Robustness
RAW	69-83 % *AFCL*	3.16 ± 2.06 s	93.4 ± 15.8 %
LAA	68-82 % *AFCL*	7.11 ± 5.08 s	99.4 ± 1.7 %
I	~76 % *AFCL*	8.30 ± 7.36 s	26.3 ± 19.7 %
PV	70-83 % *AFCL*	3.65 ± 3.34 s	93.4 ± 6.8 %
S	68-77 % *AFCL*	7.31 ± 7.21 s	46.8 ± 28.9 %

No significant difference was observed between the Time to Capture values at the different pacing locations. Significantly higher Capture Robustness values were found at RAW, LAA and PV locations compared to I and S ($p<0.001$) and for LAA compared to PV ($p=0.027$).

Fig. 4 shows the spatial repartition of wavefronts following capture for the different pacing locations (captured areas). Although at some of the pacing locations fast and robust capture was obtained, with a captured area encompassing the major part of the paced atrium, this was often accompanied by residual reentrant waves outside the captured area. Based on our observations, the best sites to gain capture in either the RA or the LA are located distally from obstacles such as RAW and LAA. This preference for the right atrial lateral wall in the RA was also observed in clinical data [5]. When pacing only in one atrium, control in both atria was not observed. Only pacing at S led to capture of both atria, albeit showing a low Capture Robustness. Due to its location between the inferior vena cava and the tricuspid valve, only brief episodes of capture could be observed for site I and reentrant waves were often present around the inferior vena cava.

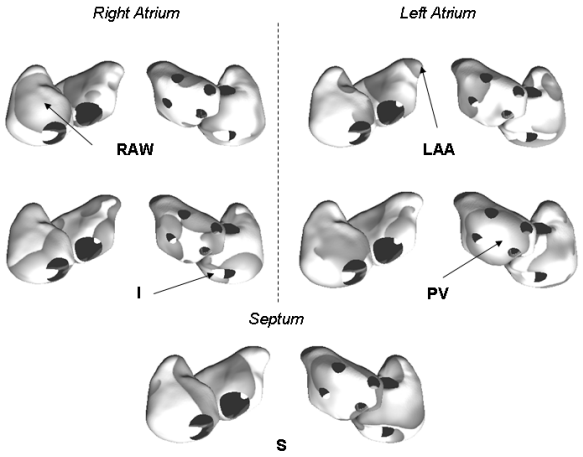

Fig. 4. Representation of captured areas for the five pacing sites for burst pacing at optimal *PP*. The pacing sites are indicated with an arrow, except for the septum where the pacing site is not visible.

The different steps leading to capture in the RAW are shown in Fig. 5, showing how burst pacing gradually takes control of the RA. In this example, after 3220 ms of pacing, capture was achieved in the RA (about 83 cm^2), but several reentrant wavelets were still present in the LA and AF did not terminate. This observation is consistent with experimental data [3].

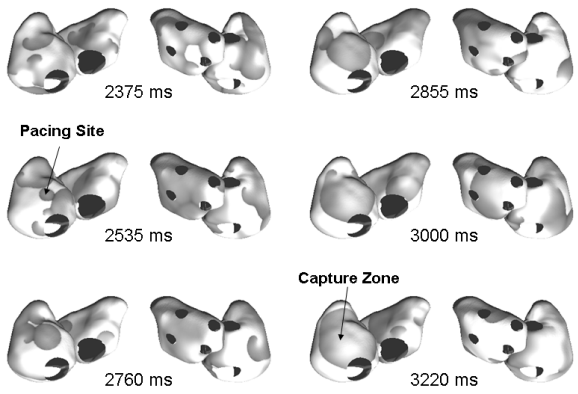

Fig. 5. Example of burst pacing at 80 % *AFCL* in the RAW until capture is obtained. Below each snapshot showing the atrial electrical activity, the time elapsed from the beginning of pacing is indicated.

Fig. 6 and 7 compare the capture results for burst and ramp pacing in the RAW. It shows that for burst pacing, for *PP* values within the Capture Intervals, the Time to Capture is comparable at all *PP*s. When *PP* was increased to values outside the Capture Interval, Capture Robustness decreased and a gradual loss of capture was observed, due to the penetration of reentrant wavelets in the captured area. Burst pacing induced a local control of AF at a faster rate than the original AF, but termination was not possible due to the fact that a slowing down of the pacing rate allowed these residual wavelets to provoke loss of capture.

Incremental ramp pacing prior to burst pacing increased

the Time to Capture for decreasing values of *PP* (Fig. 7): in the RAW, the addition of this transient ramp significantly increased the Time to Capture to 9.25±5.8 s (p=0.012). This means that ramp pacing did not result in a gradual capture of AF and that scanning through different pacing rates in fact weakens the ability to capture AF. However, this transient ramp before fixed period pacing did not effect Capture Robustness.

Published results from comparative clinical studies in humans on ramp and burst pacing for atrial arrhythmias are sometimes contradictory. Furthermore there is a difference between the reported high rate of ATP efficacy and the failure to demonstrate a reduction of AF burden with ATP. Gulizia et al. found that ramp led to a higher termination efficacy than burst but for slower and more organized atrial tachyarrythmia [11]. However, there is no evidence that this is valid for AF. Our study suggests that the ATP algorithms working well for slower atrial tachyarrythmias cannot be directly transposed to AF, which is faster and less organized.

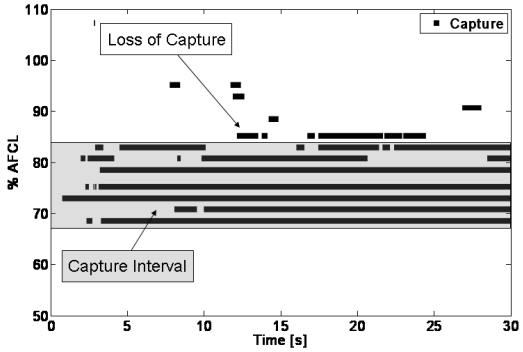

Fig. 6. Burst pacing in the RAW for *PP* in the range 20-110 % *AFCL* (computed on the three AF initial conditions). Time during which capture is obtained is indicated by thick black lines. The Capture Interval is highlighted in grey.

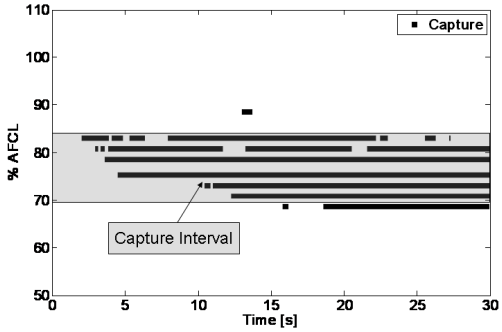

Fig. 7. Ramp pacing in the RAW for *PP* in the range 20-110 % *AFCL* (computed on the three AF initial conditions). Times during which capture is obtained are indicated as thick black lines. The Capture Interval is highlighted in grey.

IV. Conclusion

Our study of existing ATP protocols based on a complete representation of atrial geometry permits a systematic evaluation of AF under controlled conditions and has access to all variables of interest at any time. The optimal pacing period was similar for all pacing sites studied when computed as a percentage of the *AFCL* measured at the pacing location (68-83 %). Pacing sites located away from obstacles to propagation led to a faster and more robust capture. Obtaining capture of both atria was found possible only when pacing in the septum, although being far less robust. Our results involving ramp pacing simulations indicate that it is necessary to pace at a fixed optimal period over a sufficient long time to gain capture during AF. This model will be used to further develop new pacing algorithms.

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