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Use of a biophysical model of atrial fibrillation in the interpretation of the outcome of surgical ablation procedures☆

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Abstract

Objective: To determine the adequacy of '*in silico*' biophysical models of atrial fibrillation (AF) in the design of different ablation line patterns. **Background:** Permanent AF is a severe medical problem for which (surgical) ablation is a possible treatment. The ideal ablation pattern remains to be defined. **Methods:** Forty-six consecutive adult patients with symptomatic permanent drug refractory AF underwent mitral surgery combined with non-transmural, (n = 20) and transmural (n = 26) radiofrequency Minimaze. The fraction of '*in vivo*' conversions to sinus rhythm (SR) in both groups was compared with the performance of the fraction of '*in silico*' conversions observed in a biophysical model of permanent AF. The simulations allowed us to study the effectiveness of incomplete and complete ablation patterns. A simulated, complete, transmural Maze III ablation pattern was applied to 118 different episodes of simulated AF set-up in the model and its effectiveness was compared with the clinical results reported by Cox. **Results:** The fraction of conversions to SR was 92% '*in vivo*' and 88% '*in silico*' (p = ns) for transmural/complete ablations, 60% respectively 65% for non-transmural/incomplete Minimaze (p = ns) and 98% respectively 100% for Maze III ablations (p = ns). The fraction of conversions to SR '*in silico*' correlated with the rates '*in vivo*' (r^2 = 0.973). **Conclusions:** The fraction of conversions to SR observed in the model closely corresponded to the conversion rate to SR post-surgery. This suggests that the model provides an additional, non-invasive tool for optimizing ablation line patterns for treating permanent AF.

Keywords: Atrium; Fibrillation; Ablation; Surgery; Biophysical modeling

1. Introduction

Atrial fibrillation (AF) is a severe and growing medical problem which has been qualified as being one of newly emerging epidemics of cardiovascular disease [1]. Several treatment options are available, aiming at restoring sinus rhythm (SR) or controlling heart rate in order to prevent stroke and heart failure: drug therapy, electrical cardioversion, catheter ablation and surgery [2,3]. After maturation of his Maze procedure, Cox et al. reported excellent results in restoring SR as well as in preventing stroke in the long-term outcome [4—6]. Although new developments in the surgical approach have reduced morbidity through less extensive procedures, it is still mainly reserved for patients eligible for concomitant cardiac surgery [7]. The AF ablation procedures aim at creating lines of conduction block to interrupt potential reentry pathways, or to eliminate foci generating ectopic beats, a source of frequent paroxysmal AF [8].

Although surgery reports high success rates, the ideal location and number of ablation lines, their best interconnection and appropriate length remain to be determined. In order to maintain the best mechanical activity of both atria during SR, a restricted number of atrial lesions is mandatory. Animal models have been utilized for studying atrial arrhythmia induction and ablation.

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; SR, sinus rhythm; RF, radiofrequency; APD, action potential duration; TAFT, time to atrial fibrillation termination; MV, mitral valve; DV, double (aortic and mitral) valve; TV, tricuspid valve; IVC, inferior vena cava; CPB, cardiopulmonary bypass; ACC, aortic cross clamping; LAA, left atrial appendage; RAA, right atrial appendage

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Advanced computer technology brings highly sophisticated biophysical models of AF [9—11]. These models allow the simulation of the complexity of the mechanisms involved in AF, which leads not only to a better understanding of its pathophysiology but also opens up innovative approaches to simulate potential treatment outcomes '*in silico*' [12—14].

This paper reports on the validation of a biophysical model of AF ablation procedures based on magnetic resonance images of the human atria. This model contains the major anatomical anchors affecting the propagation and maintenance of the electrical activation. It has the potential to become an important contributor in improving the understanding of how to interrupt permanent AF.

2. Methods

2.1. Patients' characteristics

Between May 1998 and June 2003, 2948 adult patients underwent elective heart surgery in our Department. Forty-six consecutive adult patients underwent mitral surgery through a left atriotomy (the primary indication) combined with a so-called Minimaze procedure because of associated permanent AF [15]. The patients were divided into two successive groups: Group I with endocardial RF application ($n = 20$) and Group II from April 2000 with endo- and epicardial, supposedly transmural RF application ($n = 26$). Detailed patient and surgery characteristics are shown in Table 1.

2.2. Surgical ablation procedure

Surgery was performed under moderate hypothermic cardiopulmonary bypass using antegrade intermittent cold blood cardioplegia. The left atrial appendage (LAA) was systematically stapled and removed. The left atrium was opened parallel to the interatrial groove in a semi-circular fashion around the right pulmonary veins. Endocardial (Groups I and II) and epicardial (Group II only) applications of the electro-surgical probe Thermaline (Boston Scientific Corporation, San José, California, USA) was used for radiofrequency ablation from LAA resection edges to left atriotomy edges and to fibrous heart skeleton with two endocardial RF-application, ablation pattern described in Fig. 1. Ablation temperature was 70 °C, maximal energy output was 150 W, and duration of each RF application was 120 s. In the immediate postoperative phase, all patients were anticoagulated with IV heparin followed by oral anticoagulation with acenocoumarol (Novartis, Basel, Swit-

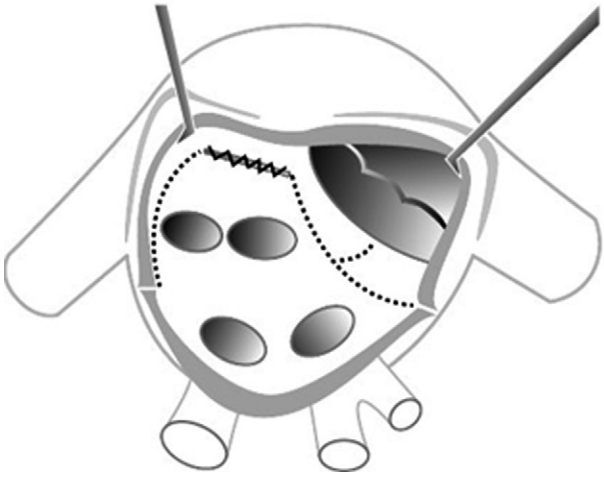

Fig. 1. Simplified Maze ablation procedure after left atriotomy. View of the opened left atrium: left atrial appendage resection (zigzag line) and radiofrequency ablation around the pulmonary veins and reaching the mitral annulus (dotted lines).

Table 1
Baseline characteristics of included patients and applied surgical procedures

	Group I	Group II	*p*-value
Patient characteristics			
Number of patients (male)	20 (60%)	26 (69%)	0.51
Age (mean ± SD, years)	63.8 ± 8.4	63.9 ± 9.2	0.95
LVEF (mean ± SD)	59 ± 8%	63 ± 10%	0.14
AF duration (mean ± SD, months)	38.4 ± 45.1	20.8 ± 43.3	0.19
Preoperative NYHA III & IV	50%	52%	0.67
Left atrial diameter (mean ± SD, mm)	58 ± 10	57 ± 7	0.95
EuroSCORE (mean ± SD)	5.0 ± 2.2	4.6 ± 2.1	0.55
Surgical characteristics			
Primary cardiac procedure			
MV repair	7 (35%)	12 (46%)	0.12
MV replacement	9 (45%)	9 (35%)	0.98
DV procedure	4 (20%)	5 (19%)	0.80
Peroperative characteristics			
Intervention duration (mean ± SD, min.)	241 ± 37	237 ± 40	0.71
CPB duration (mean ± SD, min)	145 ± 39	136 ± 23	0.31
ACC duration (mean ± SD, min)	115 ± 30	109 ± 17	0.43
Ablation procedure duration (mean ± SD, min)	19 ± 6	21 ± 4	0.22
RF energy (mean ± SD, *J*)	19,329 ± 6,104	21,152 ± 7,617	0.45
Duration of intubation (mean ± SD, hours)	17.4 ± 9.3	17.2 ± 12	0.95
Length of hospitalization (mean ± SD, days)	13.7 ± 7.4	12.3 ± 3.9	0.41

Group I: endocardial radiofrequency (RF) ablation; Group II: endo- and epicardial (transmural) RF ablation ($n = 26$). MV, mitral valve; DV, double (aortic and mitral) valve; CPB, cardiopulmonary bypass; ACC, aortic cross, clamping; RF; radiofrequency.

zerland) at discharge. Anti-arrhythmic agents (mainly amiodarone) were prescribed in the event of recurrent AF or atrial flutter during the early postoperative phase. Post-surgery follow-up visits took place at 1, 6 and 12 months, then yearly. Patients were considered clinically converted to SR or not at the 6 postoperative month. Institutional and written patient consents were obtained to perform this study.

2.3. Biophysical modeling

Since atrial geometry plays an important role during arrhythmia and ablation procedures, our biophysical model was based on magnetic resonance images of human atria [16]. The resulting surface was meshed with triangular elements and electrical propagation was solved in a mono domain cardiac tissue as described earlier [14,17,18]. At each node, a membrane kinetics model was implemented based on the Luo—Rudy model adjusted to match atrial cellular properties [19,20]. The structure is monolayer and contains holes representing the inlets of the major vessels and the atrio-ventricular valves (Fig. 2).

Ablation lines were simulated by setting the conductivity tensor to zero between the cardiac cells located on the line, thus creating ideal ablation lines, defined as continuous and transmural. Two ablation patterns mimicking non-transmural (Movie 1) or transmural (Movie 2) surgical ablation lines, corresponding to the two '*in vivo*' groups predefined. Non-transmurality was simulated in a Group I_s by introducing a single gap of 3 mm wide in the line of left isthmus (Fig. 2B). This choice is based on earlier findings documenting the preferred width, number and localization of the gaps needed to mimic non-transmural ablation [12].

The electrophysiological parameters of the membrane kinetics model were adapted to reproduce action potential duration (APD) of remodeled human atrial cells during permanent AF. Baseline APD was set to 170 ms and atrial cellular properties were in accordance with published human

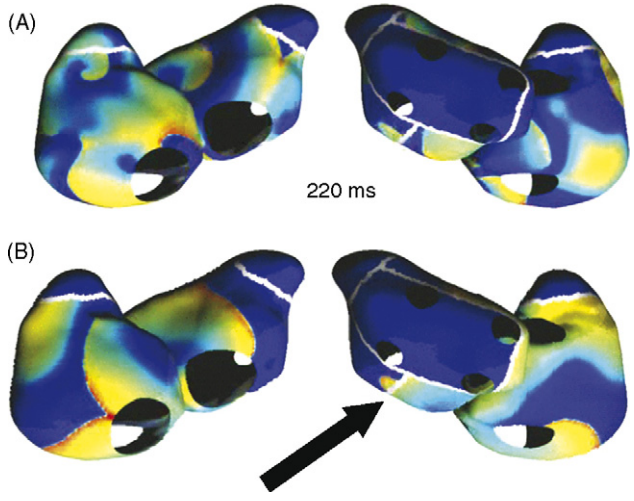

Fig. 2. Anatomical biophysical model of atrial fibrillation with the ablation lines applied during a Minimaze procedure. Ablation lines shown as white lines. (A) Complete (transmural) ablation pattern with model in atrial fibrillation with multiple wavelets. (B) Incomplete (non-transmural) ablation, simulated by a 3-mm gap in the lef isthmus ablation line (black arrow) with model in atypical left atrial flutter.

mapping data [14,21]. Sustained AF was initiated by burst pacing lasting 3 s at a frequency of 20 Hz in the sino-atrial node region, thereafter the system evolved freely. The simulated electrograms generated with these settings have been shown earlier to be consistent with observations from electrograms of patients with permanent AF [18].

Following the setting up of sustained AF, all ablation lines of the particular procedure were applied instantaneously. The time interval from the application of the lines to AF termination (time to AF termination: TAFT) was recorded, and taken as a marker of the effectiveness of the pattern. If no termination occurred within 30 s, the ablation was considered unsuccessful and longer simulations were not relevant.

Two '*in silico*' groups were defined: Group I_s with gapped and Group II_s continuous lines of conduction block, mimicking the '*in vivo*' non-transmural (Group I) and transmural (Group II) ablation patterns. Twenty and 26 simulation runs were performed at different initial conditions. In this way, different number, distribution and electrical characteristics of the wavelets constantly vary and describe the chaotic nature of AF over time. In addition, 118 simulations (Movie 3) were run for the complete transmural Maze III ablation pattern corresponding to the patient population reported earlier by Cox et al. [5].

2.4. Statistical analysis

The primary outcome was defined as the proportion of patients and simulations converted to SR after '*in vivo*' or '*in silico*' Minimaze ablation. Differences between groups were tested for significance by Fisher's exact test. Continuous variables were expressed as mean values $\pm$ one standard deviation (SD) and compared with the *t*-test. The differences in TAFT values between Group I and II was tested for significance by the one-way ANOVA method. The degree of correlation between '*in silico*' and '*in vivo*' SR conversion rates and between the '*in silico*' SR conversion rate and TAFT was assessed by correlation analysis using ANOVA to test the null hypothesis. Data analysis was performed on the JMP statistical software package from the SAS Institute Inc. (Cary NC 27513, USA), run on a Macintosh computer.

3. Results

The conversion rates of permanent AF to SR found in the 46 simulations (Group I_s and II_s) with the biophysical model were not statistically different from those observed in 46 patients who underwent mitral surgery and Minimaze (Group I and II) (Table 2). The proportions of conversion to SR after non-transmural RF ablation '*in vivo*' (Group I) and '*in silico*' (Group I_S) were the same. Thus, 60% of the patients returned to SR within 6 months after surgery, compared with 65% of the simulations run on the biophysical model (p = ns). Furthermore, the model accurately predicted the rate of simulations-patients developing an atypical left atrial flutter (AFL) and the rate of those remaining in AF compared with clinical Group I (25% vs 20%, p = ns).

Identically, 92% of the patients with transmural ablation (Group II) and 88% of the '*in silico*' simulations with

Table 2
Comparison of rhythm outcome after application of non-transmural and transmural ablation lines to patients with permanent atrial fibrillation undergoing cardiac surgery and to the biophysical AF model

Ablation pattern	Total *n*	Converted to sinus rhythm (SR)		Not converted to sinus rhythm (SR)				*p*-value converted to SR versus not
				Remained in AF		Developed atypical AFL		
		Patients (%)	Model (%)	Patients (%)	Model (%)	Patients (%)	Model (%)	
Minimaze non-transmural (Group I)	20	12 (60)	13 (65)	4 (20)	2 (10)	4 (20)	5 (25)	0.757
Minimaze transmural (Group II)	26	24 (92)	23 (88)	2 (8)	3 (12)	0	0	0.675
Group III by Cox et al.	118	116 (98)	118 (100)	2 (2)	0	0	0	0.249

continuous ablation lines (Group II_S) were converted to SR (p = ns). Eight percent of the patients versus 12% of the simulations remained in AF and none in either group developed an atrial flutter.

The conversion rates of permanent AF to SR found in the 118 simulations (Maze III_s) with the biophysical model were not statistically different from those observed in 118 patients who underwent a classical Maze III by Cox et al. [5].

Thus, the proportion of conversions to SR observed '*in vivo*' was not significantly different from the proportion of conversions predicted by the biophysical model confirming our null hypothesis. Moreover, in plotting simulations versus clinical results, we obtained a coefficient of correlation of 0.986 (r^2 = 0.973).

Mean TAFT value obtained with the biophysical model was 14.2 ± 6.9 s in Group I_S, 9.1 ± 7.3 s in Group II_S ($p < 0.001$) and 1.3 ± 0.7 s in the Maze III_S Group. TAFT was inversely correlated to the rate of conversion to SR (r^2 = 0.894).

4. Discussion

The biophysical model of AF presented in this study is to our knowledge the only model with cellular and anatomical components that is able to generate sustained AF for several minutes and to allow the study of the electrophysiological consequences of ablation lines in simulated permanent AF conditions [14]. Moreover, the comparison of '*in silico*' results to clinical outcomes observed in patients who underwent RF ablation of AF should enable us to validate our biophysical model regarding his ability to predict the effects of different ablation patterns. Indeed, no statistically significant difference was observed between tested groups, bringing a confirmation of the null hypothesis which basically aims this study.

The Maze procedure described by Cox et al. [4] has become the established gold standard for the surgical treatment of AF. It has been shown to decrease the risk of stroke, possibly due to the restoration of SR and active blood transport. As shown in an earlier publication, the application of the Maze-III procedure to the biophysical model in 118 runs resulted in a 100% conversion rate to SR (Table 2). These results were consistent with the 98% conversion rates found in the Maze-III patients' population published by Cox et al. [5]. In the present study, conversion rate to SR with the Minimaze procedure reached 88% in the biophysical model in the case of complete ablation lines (Group II_S). This result is not significantly different from the one obtained in the corresponding clinical Group II (92%), this lower performance compared with the gold standard could be possibly due to the presence of additional ablation lines in the right atrium in Maze III. Additionally to animal models, the computer model allows us to observe a gradual decrease in the number of wave breaks and a general reorganization of electrical activity, progressively preceding AF termination. In the case of the Maze-III procedure, this effect occurs very rapidly, while for the Minimaze, we could observe an important residual activity in the right atrium.

Another important aspect is transmurality of the barrier-lesions. Formerly, Group I had only endocardial RF ablation which was often non-transmural. In order to improve the procedure, our next patients constituting Group II had both endocardial and epicardial RF application on the same pattern of ablation lines. We thought this dual RF application could increase depth of lesions and afford better transmural lesions. The difference was simulated by placing a gap in the line connecting the pulmonary veins and the mitral valve annulus (Group I_S). The gap width was chosen to allow wave front propagation. Preliminary studies showed that the position of the gap along the line did not significantly affect AF termination rate [12]. Furthermore, these studies showed that other lines were less sensitive to gaps, for example around the pulmonary veins. Simulations with a conducting gap in Group I_S revealed an important rate of uncommon flutter around the vestibulus (25% of AFL), which was also observed in the clinical group (20% of AFL).

During simulations, the mean time to AF termination has been analysed. This parameter cannot be measured in clinical or experimental practice. We observed that its value was inversely correlated to the fraction of conversions to SR. Indeed, for the Maze-III procedure the mean TAFT was 1.3 s indicating a quick AF termination with little variance between the different cases. For Group II_S and I_S with a conversion rate to SR of 88% and 65%, the mean TAFT was 9.1 s and 14.2 s, respectively, with increasing variance, probably due to the complex AF dynamics present in these simulations.

The design of the biophysical model used in the present study was based on a trade-off between realism and required computation time [22,23]. On the one hand, the design needed to be complex enough to allow simulations that take into account cellular and anatomical features, and permit the study of selected AF ablation patterns. On the other hand, the model was simplified to the level needed to keep the computational load within the feasibility limits set by available computer technology [12]. In its current developmental stage, 1 s of simulation still requires 1 h of computing

time with a Pentium 1.4 GHz PC. Although anatomically correct, the necessary simplifications of the model imply several deviations from the pathophysiological reality of permanent AF. Despite the use of human atria MRI images, the geometry of the biophysical model was the same in all simulations, whereas the atrial anatomy differs in each patient. This difference may be relevant because we know that left atrial size is of tremendous importance in surgical treatment of AF [24]. Furthermore, the present biophysical model takes into account reentrant wavelets only and not rapid foci, originating from the pulmonary veins as demonstrated by Haissaguerre et al. [8].

RF application was performed on a cardioplegically arrested heart, though the result of the intervention can be considered as electrophysiologically effective at the time of cardiac reactivation, which corresponds to the instantaneous application simulated in the biophysical model. Simulations were arbitrarily run for 30 s after ablation, although late conversions to SR, a phenomenon sometimes observed in clinical practice, may have been missed. However, whether such late conversions correspond to a delayed effect of ablation after healing or are a consequence of the hemodynamic and anatomic changes resulting from cardiac surgery or from radiofrequency application remains unknown. Based on previous experience with the current model, 30 s was chosen as the most appropriate duration of observation.

4.1. Limitation of the study

The major limitation of the present study is that our model is fairly static between each comparative runs. The modeled atria remained unaltered in term of size and all other morphological changes like anatomical and electrophysiological remodeling due to chronic mitral regurgitation hence a non-'real life' imitation. An other limitation is the assumption that barrier-lesions are non-transmural in Group I and complete in Group II radiofrequency ablation pattern. Actually we have no possibility to verify transmurality of radiofrequency lesion in clinical settings. Only Cox' clinical series had real transmural lesions set with the cut-and-sew technique and therefore is fully comparable.

However, due to limitation of processor power our model is the only one which is useful to study chronic substrate of atrial fibrillation met in surgical patients. The next improvement will be the use of a personalized model based on each patient's own MRI in a multilayer model.

5. Conclusion

In comparing between patients who underwent associated Minimaze procedure and simulations on a biophysical model of AF we were able to identifiy a positive correlation between clinical result and our '*in silico* model' of AF for both SR conversion and residual atrial flutter rates. These encouraging results suggest that our biophysical model of permanent AF is a valuable tool to search for the optimal effective ablation pattern with the least impairment of the atrial function and impulse conduction.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcts.2007.02.031.