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# **PhD THESIS**

**ULTRAHIGH DENSITY SEQUENTIAL MAPPING  
OF PERSISTENT ATRIAL FIBRILLATION**

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## **SUMMARY**

Atrial fibrillation, the most common of cardiac arrhythmias, is one of the major problems facing healthcare systems worldwide because it is a chronic disease without cure and which involves both a significant morbidity and mortality and a marked decrease in the quality of life of these patients.

Atrial fibrillation is defined by the total disorganization of the atrial electrical activity of the heart and is the result of complex phenomena of fibrosis and inflammation. These lead to an electrical remodelling that initially disrupts the normal electrical circuit (by forming re-entry circuits) and then gradually degrades atrial activity to the final stage of being totally disorganized.

The main mechanism underlying atrial fibrillation is a first electrical remodeling of the atrial wall structure, a complex process characterized by the activation of fibroblasts, by exaggerated deposits of connective tissue and especially by an exaggerated phenomenon of fibrosis. This process begins several years before the first clinical manifestations. Structural remodelling disrupts the electrical circuits at the level of the atrial tissue, favouring local re-entry phenomena ("micro-re-entries") that thus perpetuate arrhythmia. Other phenomena involved at the structural level are: fatty infiltration, inflammatory infiltration, hypertrophy of myocytes, necrosis and even amyloidosis. All these functional and structural changes in the atrial myocardium result in a prothrombotic status. Even short episodes of atrial fibrillation can lead to myocardial tissue damage, triggering prothrombotic factors at the surface of the atrial

endothelium which, together with the thrombocytic and inflammatory activation, contributes to a generalized prothrombotic state.

Regarding the medical treatment of atrial fibrillation, the greatest advances of the last 10-15 years have been made in the field of anticoagulant treatment. With the understanding of the pathophysiological mechanism by which atrial fibrillation increases the thromboembolic risk leading to strokes, it has become clear that strokes represent the most serious complication and therefore the most feared in the cases of atrial fibrillation. Thus, anticoagulant treatment has become a therapeutic priority which lead to the emergence of new classes of drugs. During this time, the medical treatment of atrial fibrillation episodes has made much more moderate progress: the classes of antiarrhythmic drugs have remained largely the same over the last two decades.

The greatest progress that has occurred in the last 10-15 years has been with the interventional treatment: the catheter ablation of atrial fibrillation. The initial techniques focused on paroxysmal atrial fibrillation (the less advanced form of this pathology, with pathophysiological mechanism which is better understood), and after a few years of technical improvements started achieving success rates of about 80-90%. As these ablation procedures have improved and they have become safer and easier to perform, the focus has gradually shifted to patients suffering from persistent atrial fibrillation, a category excluded at the beginnings of this invasive procedure. However, because persistent atrial fibrillation has an incompletely understood pathophysiology, the success rate of persistent atrial fibrillation ablation is now much more modest (40-60%).

The technology used in the catheter ablation procedure regarding the mapping of the electrical activity (identification and

positioning in three-dimensional space of the local electrical signals from the cardiac depolarization) has seen an exponential progress: if a decade ago the mapping systems recorded several tens of local electrocardiograms with their localizations in a three-dimensional reconstruction of the cardiac chambers, the latest mapping systems are capable in 2019 of a very high resolution: recording and positioning in the three-dimensional space tens of thousands of local electrocardiograms with better quality and accuracy of the electrical signal itself.

The present study comes from the confluence of this possibility (the ultra high resolution mapping system) with the need described above (increasing number of patients with persistent atrial fibrillation with limited therapeutic options).

The objective of this study was to test the hypothesis that ultra high resolution mapping of persistent atrial fibrillation (patients with no previous radiofrequency ablation procedures in the left atrium) can provide new and useful information both for understanding the mechanisms of the electrophysiological maintenance of persistent atrial fibrillation as well as radiofrequency ablation guidance beyond electrical isolation of pulmonary veins for the clinical purpose of improving short-term outcomes (stopping atrial fibrillation either by returning to sinus rhythm or by organizing in atrial tachycardia) and long-term (1 year freedom from atrial fibrillation).

The study group consisted of all patients with an indication for ablation of persistent atrial fibrillation who were scheduled for a procedure in section cardiology department of hospital *Center Hospitalier Princesse Grace Monaco* and who gave informed consent for the procedure.

The criteria for inclusion in the study were:

- presence of persistent atrial fibrillation
- indication for persistent atrial fibrillation ablation in accordance with the European Heart Rhythm Association Guidelines.

The exclusion criteria from the study were:

- history of atrial fibrillation ablation (or any ablation in the left atrium);
- presence of sinus rhythm or atrial tachycardia at the beginning of the procedure;
- refusal to sign the consent form;
- technical reasons: patients were excluded when the recorded atrial fibrillation dominant cycle length " was  $<150\text{ms}$ .

The anti-arrhythmic treatment was interrupted with at least five half-lives; amiodarone being discontinued 1 month before the procedure.

All patients received a preoperative evaluation by trans-thoracic echocardiography. A CT scan or MRI was also performed pre-operatively with the three – dimensional reconstruction of the left atrium. Clinical and paraclinical data such as age, sex, years of atrial fibrillation, duration of current episode of persistent atrial fibrillation, risk factors and comorbidities were collected. During the procedure, information was collected about the electrical activity of atrial fibrillation (such as local voltage, cycle length or surface of the atrium with synchronous activity) and about ablation shots (energy used, radiofrequency time, etc.). Long-term data were collected through follow-up visits (with 12 lead ECGs and with the regular use of heart rate monitoring via Holter ECG / 24 hours) and by telephone communication with patients or their cardiologists.

51 patients (mean age 64 years, 28% women) were included in the study group. For each patient, at least 3 successive maps of the left atrium were made (one initial map, one after the electrical isolation of the pulmonary veins and a third map after the first series of ablation points of the identified activity areas).

Following the first ablation stage, a statistically significant increase of the cycle length was obtained by almost 10 ms ( $p = 0.02$ ) and with a relative extension of the organized surface by 50% ( $p = 0.01$ ). After the second mapping, there was a significant reduction of the areas of interest (the "drivers"), those with rotational or focal activity. From the point of view of the characteristics of the areas identified as rotational and focal, we found that the rotors covered a larger percentage of the cycle length (the notion of " *duty cycle* " represents the percentage of the length of the local electrical activation cycle in which the rotor has clear local electrical activity). The bipolar electrogram in the center of the focal activity had a much greater amplitude (0.50mV) than the bipolar electrogram in the center of the rotor (0.16mV), and the duration of the electrogram (EGM) in the center was considerably longer in the case of the rotor compared to the focal type activity. All of these differences were statistically significant ( $p < 0.0001$ ). From the point of view of the location of these areas of activity in the left atrium anatomy we observed that more than 50% of the rotors and the focal activities were concentrated in the anterior wall (28%) and at the lower part of the posterior wall ( 27%) .

For the ablation, the radiofrequency time for pulmonary vein isolation was  $2239 \pm 801$  seconds. Subsequently, on average  $719 \pm 492$  seconds of radiofrequency were required while patients were still in atrial fibrillation.

This strategy resulted in 76% success in the short term (defined as stopping of the episode of persistent atrial fibrillation during the procedure or within the next 48 hours without the use of antiarrhythmic medication or electrical cardioversion) and 86% success at 1 year (defined as freedom from atrial fibrillation recurrence) .

Partial results from this study attracted the attention of the manufacturer of the mapping catheter Orion (Boston Scientific ) which started developing an algorithm that will use the data obtained in this study to automate (and possibly even optimize) the process of identifying rotor and focal type activities.

For this purpose in 2018 and 2019, some of the data obtained during the procedures were used to prepare the algorithm by a team in the research and development department of Boston Scientific .

Thus, the results of the study have already proved a first practical implementation through the algorithm that aims to improve the high resolution mapping system currently on the market.

In the near future, a prospective study is planned to compare this technique performed "manually" (identification of rotational and focal activities by the operator) with the algorithm developed by the research and development team. If validated, the algorithm will be integrated into the standard software of the Rhythmia mapping system so that it can be used worldwide in procedures of persistent atrial fibrillation ablation. At that stage, a multicenter randomized study protocol will be established to confirm efficacy.

Thus, the study fulfilled the objective of deepening the electrophysiological understanding of persistent atrial fibrillation by describing the rotational and focal type activities (proving the connection with the mathematical models of rotor) , demonstrating the practical utility from a clinical point of view ( by the fact that the radiofrequency ablation of these drivers improves the chances of achieving and maintaining the sinus rhythm ) and led to the development of an automated algorithm that will be clinically validated and then introduced as a software update in the mapping system currently on the market.