Catheter ablation of atrial fibrillation- Predictors of ablation outcome and therapeutic opportunities beyond empiric isolation of the pulmonary veins

Summary of PhD Thesis

Dr Judit Szilagyi

Thesis advisors:

Prof. Dr. Tamás Forster D.Sc., FESC, FACC, FAHA

Dr. László Sághy D.Sc.

Clinical Medical Sciences Doctoral School

Clinical and Experimental Study of Heart Disease PhD Programme

2nd Department of Internal Medicine and Cardiology Centre

University of Szeged

2021

Introduction

Atrial fibrillation (AF) is an extensively studied arrhythmia that has a significant impact on morbidity, mortality and healthcare costs. Catheter ablation of AF, performed since the late 1990s is a reasonable alternative to antiarrhythmic drug therapy in nonvalvular AF. There are ongoing efforts to improve patient selection and the technique of AF ablation beyond the empiric antral isolation of the pulmonary veins (PVI) with demonstration of conduction block, currently regarded as the cornerstone of AF ablation. Nevertheless its success rate lags behind those of other electrophysiological procedures, and its complication profile is less favorable. Understanding the mechanism of paroxysmal and especially the permanent or chronic forms is key in order to find more effective therapies and to improve patient selection.

The main factors to consider when deciding on individualized therapy are type of AF and duration of continuos AF, extent of atrial remodeling as evidenced by cardiac MRI, voltage mapping, left atrial size or electrophysiological measurements (such as DF, organizational index of fibrillatory activity), presence and control of modifiable risk factors (such as BMI, diabetes, hypertension) and individual procedural risk factors. These might identify subsets of patients thought not to benefit as much from PVI or in whom more extensive substrate modification or hybrid thoracoscopic surgical and transvenous catheter ablation should be considered such as ones with severe mitral valve disease, long standing AF, overt chronic obstructive pulmonary disease or severe sleep apnea. However, there are reports of successful ablations in patients to whom ablation therapy was not customarily offered in the past, such as patients with congenital heart disease, hypertrophic cardiomyopathy or heart failure. Data suggest that PVI improves heart failure in terms of quality of life, B-type natriuretic peptide levels as well as mortality.

Part I

The first part of my thesis details how the spectral characteristics of AF reflect atrial remodeling and predict catheter ablation outcome.

Background

It is well known that persistent AF leads to progressive electrical remodeling, shortening of the effective refractory period and fibrillatory cycle length, along with structural remodeling marked by progressive fibrosis. Such changes may be reflected in the frequency spectra of fibrillatory electrograms. Features of the AF spectrum have been shown to correlate well with cycle-length data, but their predictive value is inconsistent across studies and unsuitable for screening purposes due their low performance and cumbersome nature. In the first part of our project we sought to investigate whether parameters derived from the spectral analysis of surface ECG and intracardiac AF electrograms can predict outcome in patients referred for pulmonary vein isolation (PVI) with the potential to improve patient selection and guide ablation strategy.

Methods

We performed spectral analysis on the surface ECG and intracardiac electrograms from patients referred for AF ablation at the University of California, San Francisco from July 2011 to May 2016. Thirty seconds of continuous AF prior to RF ablation were selected and digitally exported for analysis from the distal and proximal poles of the coronary sinus catheter as well as from the RA and His catheters. Surface ECG signals were recorded from leads V1, aVL, V5 or V6 as well as one of the inferior leads. After filtering and QRST subtraction, we performed a Fast Fourier analysis and we measured the dominant frequency (DF), regularity index (RI) and the organizational index (OI) of fibrillatory electrograms and determined their value for predicting AF recurrence after ablation. Additionally, three experienced electrophysiologists were asked to classify 10 s AF segments “fine”, “coarse,” or “indeterminate” based on fibrillatory wave appearance, and make a prediction regarding the outcome of the PVI (success or failure).

Patients were all discharged with a 4-week event monitor and underwent 2 week continuous monitoring at 6 months and 1 year and were seen in clinic at 1 month, 6 months, 12 months and every 6-12 months thereafter.

We defined ablation success as no AF or rare AF (not more then 1 spontaneously terminating AF episode, lasting <24 hours, within 6 months) off antiarrhythmic drugs. For patients without documented AF recurrences at 6 months, antiarrhythmic drugs were discontinued.

Results

We analyzed data from **153 PVI procedures in 140 patients**. The mean age was 62.1±9.2 years, 71% were male, and 67.1% of patients had persistent or longstanding persistent AF.

DF was higher in persistent compared to paroxysmal AF, and OI was generally lower in persistent compared to paroxysmal AF both on the surface ECG leads as well as analyzing intracardiac recordings from the distal and proximal coronary sinus as well as the His/RA sites. There was a good correlation betwen the surface ECG spectral indices and those derived from intracardiac electrograms, DF in V1 correlated best with CSp (r=0.76, p=0.0001) and DF in aVL correlated best with CSd (r=0.78, p=0.0001).

66.7% of patients wth paroxysmal AF had a positive **left-to-right atrial DF gradient** compared to 40% of persistent AF patients (p=0.061).

Over a median of 10.1 months of follow-up, **AF recurrence** was observed in 97 patients.

In a multivariable model, **DF in the right atrium (RA)** and **distal coronary sinus (CSd)-to-RA DF gradient** predicted AF recurrence (OR=3.52, p=0.023 and OR=0.2, p=0.034, respectively). DF in RA and CSd to RA DF gradient had a good predictive value for PVI outcome (AUC of 0.73, p=0.007 and 0.74, p=0.007, respectively).

Of the clinical variables (age, gender, BMI, type of AF, history of hypertension, coronary artery disease, cardiomyopathy, and prior congestive heart failure) **a higher BMI** (OR=1.085, 95% CI 1.01-1.168, p=0.031) and **persistent AF** (OR=4.09, 95% CI 2-8.34, p=0.0001) was predictive of AF recurrence, however, this was not an independent predictor of AF recurrence when spectral parameters were included in the model.

Predicton of ablation outcome based on the **visual classification of fibrillatory appearance** was poor.

Part II

Background

Recurrence of AF after PVI is largely due to the reconnection of the pulmonary veins, but with advances in techniques that ensure a better catheter contact and lesion formation, a growing number of patients are returning to the EP lab with recurrent AF despite the persistent isolation of the pulmonary veins (PVi patients). The study of the aforementioned patient population might shed light on the involvement of non-PV triggers in AF and the usefulness of additional ablations. **Definition of the PVi patient population, ablation strategy and outcomes in this group is the subject of the second part of my thesis.**

Methods

We studied consecutive patients with recurrent AF undergoing repeat ablation at the University of California, San Francisco (UCSF) from July 2011 to July 2016 and compared patients with PVi (patients with isolated pulmonary veins) to those with PVr (reconnected pulmonary veins).

All patients had previously undergone at least one PVI or, in some cases, surgical ablation. PV reconnection was checked for every patient. The ablation approach was left to the discretion of the electrophysiologist performing the procedure. Ablation lesions were delivered using an irrigated catheter with power ranging from 20-30W. When ablation on the posterior wall was performed, the temperature was measured via an esophageal temperature probe. Anticoagulation and TOEs and preprocedural atrial imaging were performed according to local and international guidelines.

PVr patients

If PV reconnection(s) were present, reisolation of the PVs was performed with demonstration of entrance and exit block. Additional ablation targetting any spontaneous or isoproteronol induced

provoked AF triggers was performed. Empiric substrate modification was not typically performed in this group.

PVi patients

For PVi patients, a systematic protocol for targetting potential non-PV triggers was employed including 1) ablation of any spontaneous atrial tachycardias or flutters, 2) incremental doses of isoproterenol up to 20 μg/min to identify any non-PV triggers of AF or consistent atrial premature beats, or 3) any atrial tachycardia/flutter induced with burst atrial pacing (250-200ms, decrementing by 10ms, for 5 seconds each). Additional ablation such as box isolation of the left atrial posterior wall, antral extension of previous ablation lines or substrate ablation was performed at the operator's discretion.

Patients were all discharged with a 4-week event monitor and underwent 2 week continuous monitoring at 6 months and 1 year. Patients were seen in clinic with an ECG at 1 month, 6 months, 12 months and every 6 months thereafter.

We defined ablation success as no AF or rare AF (not more than 1 spontaneously terminating AF episode that lasts less then 24 hours within 6 months) on or off AADs. For asymptomatic patients without documented recurrences at 6 months, AADs were discontinued.

We compared the demographic and clinical characteristics of PVi and PVr patients. We classified PVi patients according to 1) clinical presenting arrhythmia and 2) type of ablation performed. Outcomes were assessed with binomial logistic regression and Kaplan-Meier survival analysis; predictors of AF recurrence were identified with univariable and multivariable survival analysis using Cox's proportional hazards model. A P value ≤ 0.05 was considered statistically significant. Analyses were performed using SPSS software.

Results

One hundred fifty-two patients underwent repeat ablation, and of these, 25 patients (16.4%) had PVi (8.9% of paroxysmal AF and 32.7% of persistent AF patients).

PVi patients

Patients with PVi compared to PVr were more likely to have a history of persistent AF (64% vs. 26%; p<0.0001), obesity (BMI 30.4 vs. 28.2; p=0.05) and prior use of contact force sensing catheters (28% vs. 0.8%, p<0.0001).

PVi patients' (n=25) presenting arrhythmia during the repeat procedure included sinus rhythm with intermittent AF (n=12), persistent AF (n=4), or AT/AFl (n=9).

The first group (**patients presenting in SR with intermittent AF**, n=12) underwent ablation targetting isoproterenol induced AF triggers (such as from the SVC, crista terminalis, fossa ovalis, para-Hisian region, base of RA appendage, LAA, ligament of Marshall (LOM), CS), atrial substrate (antral expansion of the ablation line, CFAE ablation, posterior wall isolation, creation of ablation lines including CTI, roof line and posterolateral line to the mitral annulus) or inducible atrial tachycardias or flutters.

In PVi patients **presenting in persistent AF** (n=4) there were no triggers elicited after cardioversion with isoproteronol and so mainly had substrate modification including posterior wall isolation, CFAE ablation, empiric SVC isolation, redo of previous surgical lines with gaps, etc.

The third group comprised of 9 patients with **flutters or focal atrial tachycardias at baseline** (n=3) **or induced with isoproteronol or burst pacing** (n=6) had ablations targetting ATs originating from sites such as the Eustachian ridge, cavotricuspid isthmus, but also from LA sites such as the LAA, etc. as well as flutters with the creation of 4 CTI lines, 5 roof lines, 6 posterolateral and 3 anteromedial lines for mitral annular flutter as well as 3 septal ablation lines. In some cases (6/9 patients), additional empiric RF ablation was performed including antral expansion of the PV isolation line (n=2), CFAE ablation (n=4), SVC isolation (n=2), rotor ablation (n=1).

PVr patients

Patients with PVr underwent segmental reisolation of the PVs (mean of 3.0±1.0 PVs), which was successful in 97.6% of patients; in 3 patients one PV could not be isolated despite extensive ablation. In addition, ablation targeting non-PV triggers (n=8, 6.3%) as well as linear ablation of macroreentrant flutters was performed (n=36, 28.3%). CFAE ablation was rarely performed (n=6, 4.7%).

After a mean follow-up of 19±15 months, 56% of PVi patients remained in sinus rhythm compared to 76.3% of PVr patients (p=0.036). In a multivariable model, PVi patients and those with cardiomyopathy had a higher risk of recurrent atrial tachyarrhythmias (HR=3.6 95% CI 1.6-8.3, p=0.002 and HR=6.2, 95% CI 2.3-16.3, p<0.0001, respectively).

PVi patients with intermittent AF presenting for redo ablation in sinus rhythm (n=12) had the best outcome: freedom from AF in 9 patients (75%). In patients presenting with persistent AF (n=4), only one patient had long-term AF freedom; all recurrences were AF. In the group presenting in AT/AFl (n=9), 4 patients remained free from AF (44%), 2 had recurrent AF and 2 had recurrent atypical flutter. In one patient, both AF and atypical flutter was noted.

Part 3

The third part of my thesis is a review of the relevant literature on **predictors of catheter ablation** success (looking at comorbidities such as diabetes or OSA) as well as on **markers of progression of atrial remodeling** (such as extent of scar tissue visualized with cardiac MRI, LA strain and stiffness index, etc).

Summary and key findings

1. In the first study (Surface ECG and intracardiac spectral measures predict atrial fibrillation recurrence after catheter ablation. Szilagyi J et al., J Cardiovasc Electrophysiol. 2018) we attempted to find spectral measures of the surface ECG in AF that could be used as simple, widely accessible tools for patient selection for AF ablation, however only the organizational index (OI) in the inferior leads had a predictive value close to significance. Prediction of PVI success based on the visual evaluation of the fibrillatory activity proved to be highly subjective and unreliable. Only spectral measures derived from the intracardiac electrogram, namely higher RA dominant frequency, lower CSd to RA DF gradient had a good predictive value for AF recurrence and were significant despite the variability in AF substrate and ablation technique.

2. By performing the spectral analysis of intracardiac tracings we were able to detect the structural remodeling of the atria that leads to a higher AF recurrence rate after ablation and suggests a more remodeled atrial substrate. While not available before ablation, such measures could still be used to identify those patients who might benefit from additonal substrate modification beyond PVI in order to achieve a better outcome. In our analysis, 14 out of 43 patients with RA recordings had an RA DF>6, which was 94% predictive for recurrence after PVI. Such patients may benefit from more extensive ablation.

3. In the second study (Atrial Fibrillation Patients with Isolated Pulmonary Veins: Is Sinus Rhythm Achievable? Szilagyi J et al., J Cardiovasc Electrophysiol. 2017) we described the challenges of AF ablation in patients with isolated PVs (16% of patients returning for redo AF ablation, „PVi" patients) and described the ablation strategy in these patients consisted primarily of targeting non-PV triggers and atypical flutters in addition to other substrate modification.

4. In patients with ongoing AF despite isolated PVs, midterm freedom from AF was 56%, with some patients remaining on an antiarrhythmic drug. The presence of isolated PVs was an independent predictor of later AF recurrence. Those patients presenting in sinus rhythm with

provokable AF triggers fared best after redo ablation, with similar outcome to that in patients with reconnected PVs.

5. We identified a link between the prior use of contact force catheters and the emergence of PVi patients which underscores the efficacy of this technology.

Publications related to the subject of the thesis

1. Surface ECG and intracardiac spectral measures predict atrial fibrillation recurrence after catheter ablation. Judit Szilágyi MD, Tomos E. Walters MBBS, PhD, Gregory M. Marcus MD, MAS, FACC, Vasanth Vedantham MD, PhD, Joshua D. Moss MD, FACC, Nitish Badhwar MBBS, FACC Byron Lee MD, MAS, FACC, Randall Lee MD, PhD, FACC, Zian H. Tseng MD, MAS, Edward P. Gerstenfeld MD, MS FACC. J Cardiovasc Electrophysiol. 2018 Jul 17. doi: 10.1111/jce.13699. [Epub ahead of print]

2. Atrial Fibrillation Patients with Isolated Pulmonary Veins: Is Sinus Rhythm Achievable? Judit Szilágyi MD, Gregory M Marcus MD, MAS, Nitish Badhwar MBBS, PhD, Byron K. Lee MD, MAS, Randall J Lee MD, PhD, Vasanth Vedantham MD, PhD, Zian H Tseng MD, MAS, Tomos Walters MBBS, Melvin Scheinman MD, Jeffrey Olgin MD, and Edward P. Gerstenfeld MS, MD. J Cardiovasc Electrophysiol. 2017 Jul;28(7):754-761. doi: 10.1111/jce.13230. Epub 2017 Jun 23.

3. Atrial Remodeling in Atrial Fibrillation. Comorbidities and Markers of Disease Progression Predict Catheter Ablation Outcome. Szilágyi J, Sághy L. [published online ahead of print, 2020 Jul 21]. Curr Cardiol Rev. 2020; doi:10.2174/1573403X16666200721153620