[Ide írhatja a szöveget]

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

PhD thesis

Dr. Szilágyi Judit

Szeged, 2021

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Dr. Szilágyi Judit

Thesis advisors: Prof. Dr. Tamás Forster D.Sc., FESC, FACC, FAHA

Dr. László Sághy D.Sc.

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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

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Publications related to the subject of the Thesis

1. *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.

2. *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]

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

Abbreviations

AAD antiarrhythmic drug

ACT activated clotting time

AF atrial fibrillation

AFl atrial flutter

APD atrial premature depolarizations

AT atrial tachycardia

BMI body mass index

CEPAS Cardiac ElectroPhysiology Analysis System software

CFAE complex fractionated atrial electrogram

CHA2DS2-Vasc score Congestive heart failure (1 pt), Hypertension (1 pt), Age ≥75 years (2 pts), Diabetes Mellitus (1 pt), Prior Stroke or TIA or thromboembolism (2 pts), Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque; 1 pt), Age 65–74 years (1 pt), Sex category (i.e. female sex; 1 pt)

CHADS2 score Congestive heart failure (1 pt), Hypertension (1 pt), Age ≥75 years (1 pt), Diabetes mellitus (1 pt), Prior Stroke or TIA or Thromboembolism (2 pts)

CS coronary sinus

CSd distal coronary sinus

CSp proximal coronary sinus

CTI cavo-tricuspid isthmus

DF dominant frequency

DR-FLASH score diabetes mellitus, renal dysfunction, persistent form of AF, LA diameter >45 mm, age >65 years, female sex, hypertension

FFT Fast Fourier transform

LA left atrium

LAA left atrial appendage

LOM ligament of Marshall

OI organizational index

PV pulmonary vein

PVi patients with isolated pulmonary veins

PVI pulmonary vein isolation

PVr patients with reconnected pulmonary veins

RA right atrium

RI regularity index

SVC superior vena cava

UCSF University of California, San Francisco

Introduction and aims

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[1]. 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[2] 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[3]. 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[4], hypertrophic cardiomyopathy[5] or heart failure. Data suggest that PVI improves heart failure in terms of quality of life, B-type natriuretic peptide levels[6] as well as mortality[7].

In the first part of my thesis I will detail how the spectral characteristics of AF reflect atrial remodeling and predict catheter ablation outcome. 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[8], 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.

Recurrence of AF after PVI is largely due to the reconnection of the pulmonary veins[9], 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 will be the subject of the second part of the thesis.

Finally, I will conclude with a review of the literature on predictors of catheter ablation success looking at comorbidities such as diabetes or OSA as well as markers of progression of atrial remodeling including extent of scar tissue visualized with cardiac MRI or DF of fibrillatory activity.

Methods

Part 1:

Patient population

We included patients with AF presenting for pulmonary vein isolation (including redo procedures) at the University of California, San Francisco from July 2011 to May 2016 who had at least 30 s of atrial fibrillation recorded after the positioning of the catheters but before the start of the ablation. The institutional review board approved this retrospective study.

Signal acquisition

Surface ECG and intracardiac signals were recorded from patients who presented in AF on a digital electrophysiology system with a sampling frequency of 1000 Hz (Cardiolab, General Electric Medical Systems Information Technologies, Inc., Milwaukee, WI). Patients were placed under general anesthesia, and intracardiac decapolar catheters (Bard DYNAMIC XT with 2/5/2mm electrode spacing, Bard, Inc, Lowell, MA) were placed in the coronary sinus (CS) and by some operators (n=43 patients) in the high right atrium (RA), with the distal bipole just inside the superior vena cava. Thirty seconds of continuous AF prior to RF ablation were selected and digitally exported for analysis. We systematically exported signals from the distal and proximal poles of the decapolar catheter positioned in the CS, the best quality bipolar electrograms from the RA and His catheters, and signals recorded from leads V1, aVL, V5 or V6 as well as one of the inferior leads II, III, or aVF (the lead with the best quality tracing). Selection of electrograms for signal processing was based upon the amplitude of the signals suggestive of good catheter-endocardium contact; the person performing selection and analysis was blinded to the ablation outcome. Recordings of organized atrial tachycardias or flutter were excluded.

Signal processing

The digitally exported signals were imported into Cardiac ElectroPhysiology Analysis System software (CEPAS, Cuoretech Pty Ltd, Sydney, Australia) for analysis. All signals underwent additional filtering with a 60 Hz notch filter, a low-pass elliptic filter with pass frequency of 40 Hz and stop frequency of 80 Hz, as well as a wavelet filter to remove baseline wander. Signals underwent QRST subtraction to remove far field ventricular signals using the spatiotemporal QRST cancellation method[10]. The signals were then divided into 10-second epochs. Each 10-second segment underwent half-wave rectification, followed by a Fast Fourier transform (FFT) using a Hanning window and zero padding to achieve a 0.1 Hz frequency resolution (Figure 1). The dominant frequency (DF) was defined as the peak with the highest amplitude in the 3-15 Hz band of the power spectrum[11]. The regularity index (RI) is defined as the ratio of the power at the DF and its adjacent frequencies (±0.75 Hz band) to the total power of the 3-15 Hz band[12]. The organizational index (OI) is defined as the ratio of the power at the DF and its harmonics up to, but not including, the fifth harmonic peak to the remainder of the spectrum in the 3-15 Hz band[13]. The abovementioned parameters were calculated for each of the three 10-second segments and averaged.

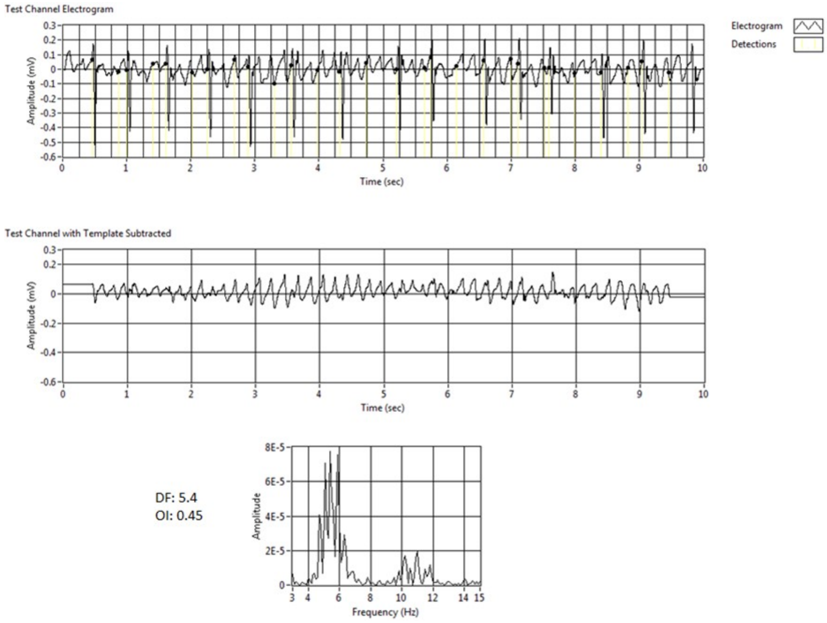


Figure 1. Signal processing. Top panel: Surface ECG in lead V1 of a patient with AF. Middle panel: the same signal after QRST subtraction shows the remainder atrial activation. Bottom panel: Frequency spectrum after FFT of signal in middle panel. The dominant frequency (DF) in this signal was 5.4 Hz and the organizational index (OI) is 0.45.

DFs in epochs with a regularity index of less than 0.2 were manually reviewed and excluded if signals were noisy or of poor quality. In order to determine if spectral measures had additive value to subjective ECG classification of AF, three experienced electrophysiologists (TEW, JDM, EPG) independently performed a blinded evaluation of surface ECG recordings corresponding to the first and last 10-second epochs of each of the 30s segments. The atrial activation during AF was subjectively classified as "fine", "coarse," or "indeterminate" based on fibrillatory wave appearance, and the outcome of the PVI (success or failure) was predicted based on the perceived fibrillatory ECG characteristics. The subjective prediction by each physician was classified as ablation "success" or "failure" if their predictions were the same for both 10-second ECGs, or "indeterminate" otherwise. We also determined whether there was a significant relationship between quantitative spectral measures of AF and subjective physician analysis, and whether the latter predicted AF ablation success for the three observers individually and for their pooled evaluation.

Catheter ablation

All antiarrhythmic drugs were held for at least 3 days prior to ablation. Patients taking amiodarone were excluded. Patients underwent antral circumferential pulmonary vein isolation using irrigated RF catheter ablation as previously described[14]. Additional ablation of AF triggers or flutters was performed at the operator's discretion.

Patient follow-up

Patients were all discharged with a 4-week event monitor and underwent 2 week continuous monitoring at 6 months and 1 year (Lifewatch Inc; Rosemont, IL). Patients were also sent monitors to document any symptomatic AF recurrences between visits. Patients 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. Patients who did not have follow-up beyond the blanking period (2 months) were excluded from the study.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation if normally distributed and median and interquartile range for non-normal distributions; categorical variables were expressed as frequencies and percentages. Student's t-test or Mann-Whitney U test and Pearson's chi-square or Fisher's exact test were used to compare between groups for continuous and dichotomous variables, respectively. We performed Pearson correlation analysis between surface ECG and intracardiac DFs, namely DF in lead II/III/aVF, aVL, V1, V5/6 and CSd, CSp, His recording/RA recordings. Outcomes were assessed using binomial logistic regression, and predictors of PVI outcome were identified with univariable and multivariable analysis with forward conditional modeling. Variables evaluated included parameters of the power spectrum from surface ECG or intracardiac signals, age, gender, body mass index (BMI), type of AF (paroxysmal, persistent or long-lasting persistent according to AHA/ACC definitions[15]), hypertension, coronary artery disease, cardiomyopathy, and prior congestive heart failure. The agreement between the predictions of the three surface ECG readers was assessed using the Fleiss' Kappa statistic. We determined the relationship between the readers' predictions and the DF value in the RA and CSd using independent samples T test and ablation outcome using binomial logistic regression. A P value $\leq$ 0.05 was considered significant. Analyses were performed using SPSS software (version 23.0, SPSS Inc., Chicago, IL).

Part 2:

Patient population

Consecutive patients undergoing repeat ablation for documented recurrent AF or regular atrial tachyarrhythmias after prior PV isolation for treating AF at the hospital of the University of California, San Francisco (UCSF) from July 2011 to July 2016 were included. Data was collected uniformly in a prospective database (Apollo LX, LUMEDX, Oakland, CA) after each procedure and analyzed retrospectively. All patients had previously undergone at least one wide area antral pulmonary vein isolation performed either at our institution or an oustide hospital, either with catheter ablation or, in some cases, surgical ablation. The ablation approach was left to the discretion of the electrophysiologist performing the procedure. Permission to publish collected data was obtained from the UCSF human research committee. All patients were anticoagulated with either warfarin or a factor Xa or direct thrombin inhibitor prior to ablation. Ablation was performed on uninterrupted warfarin or minimally interruped non vitamin-K antagonist oral anticoagulant. A transesophageal echocardiogram was performed in selected patients to rule out a left atrial thrombus. Preprocedure cardiac computed tomography or magnetic resonance angiography was performed to exclude PV anomaly or stenosis. Antiarrhythmic drugs (AADs) were discontinued for at least 5 half-lives before the procedure except amiodarone, which was stopped between 3 days and 2 weeks prior to the procedure at the attending's discretion.

Ablation procedure

All patients gave informed consent and were brought to the electrophysiology lab in a fasting state. The procedures were performed under general anesthesia. Surface ECG and intracardiac signals were recorded on an electrophysiology system (Cardiolab, General Electric Medical Systems Information Technologies, Inc., Milwaukee, WI). After obtaining venous access an intracardiac echocardiography (ICE) catheter (8Fr, AcuNav, Biosense Webster, Diamond Bar, CA) was advanced through a 9Fr sheath in the femoral vein to the right atrium, a decapolar catheter was advanced into the coronary sinus (CS), and either a decapolar catheter was advanced to the high right atrium (RA)/superior vena cava (SVC) junction or a His catheter to the AV junction. Prior to transseptal puncture, anticoagulation with unfractionated heparin was initiated and the activated clotting time (ACT) was assessed every 15 minutes to maintain the ACT between 350 and 400 seconds. After transseptal left atrial access, a circular duodecapolar mapping catheter (Lasso, Biosense Webster, Diamond Bar, CA or Spiral, St. Jude Medical, St. Paul, MN) and an irrigated mapping/ablation catheter (ThermoCool, Thermocool SF, Thermocool NaviStar or Therocool Smarttouch, Biosense Webster, Diamond Bar, CA; Tacticath St. Jude Medical, St. Paul, MN; Chilli II, Boston Scientific, Marlborough, MA) were advanced to the left atrium (LA) through an SL1 and Agilis steerable sheath, respectively. Carto (Biosense Webster, Diamond Bar, CA) or NavX (EnSite, St. Jude Medical, St. Paul, MN) electroanatomic mapping systems were utilized. A voltage map of the LA was acquired and each PV was interrogated with the circular mapping catheter to determine any evidence of PV reconnection. In the case of ambiguous signals, pacing from adjacent structures (LA appendage, posterior wall or RA) was performed to distinguish far field from PV signals[16]. In addition, pacing (10 mA, 2ms) was performed from each bipole on the circular mapping catheter placed inside each PV to determine if exit block was present[17]. Ablation lesions were delivered using an irrigated catheter with power ranging from 20-30W. When ablation on the posterior wall was performed, temperature measured via an esophageal temperature probe was monitored. Power on the posterior wall was limited to ≤25 W and ablation was terminated for temperature rise >1°C or >38.5°C.

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). Non-PV triggers of either AF or consistent atrial premature depolarizations (APDs) were regionalized and targeted for ablation using previously described techniques[18]. For any triggers within the superior vena cava, SVC isolation was performed using the circular mapping catheter to achieve entrance and exit block, unless limited by proximity to the phrenic nerve or sinus node. In patients with triggers from the coronary sinus, segmental endocardial and epicardial ablation along the region of elicited triggers was performed without completely isolating the CS. Other non-PV triggers were targeted focally. If triggers or low voltage was noted in the left atrial posterior wall, a box isolation was performed by ablating a roof line and posterior line between the inferior PVs. Bidirectional block was confirmed with pacing maneuvers and was the goal of linear ablation whenever possible. In patients where voltage mapping determined that the prior PV isolation was more distal or at the level of the PV ostium, the ablation lesions were extended to include the entire PV antrum. If antral isolation was present and if no AF triggers or flutters could be elicited, additional substrate ablation was performed at the operator's discretion. In patients who had previous left atrial lines (surgical or percutaneous), we assessed the presence of conduction block across the ablation lines and closed the gaps in the event of reconduction. Complex fractionated atrial electrogram (CFAE) ablation was performed in some patients at the operator's discretion.

Follow-up

Patients were all discharged with a 4-week event monitor and instructed to send strips daily and with any symptoms; patients underwent 2 week continuous monitoring at 6 months and 1 year (Lifewatch, Rosemont, IL). 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. Patients who did not have follow-up beyond the blanking period (2 months) were excluded from the study.

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.

Statistical analysis

Continuous variables were expressed as means ± standard deviations for data with normal distribution or median and interquartile range for skewed distribution; categorical variables as frequencies and percentages. Student's t-test or Mann-Whitney U test and Pearson's chi-square or Fisher's exact test were used to compare continuous and dichotomous variables, respectively, between groups. 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. Variables analyzed included presence of isolated veins at the time of the redo procedure, age, gender, body mass index (BMI), type of AF (paroxysmal, persistent or long-lasting persistent according to AHA/ACC definitions (7)), hypertension, coronary artery disease, prior clinical episode of congestive heart failure requiring medical therapy and cardiomyopathy (hypertrophic, dilated or post-infarction with EF<50%). A P value ≤ 0.05 was considered statistically significant. Analyses were performed using SPSS software (version 19.0, SPSS Inc., Chicago, IL).

Results

Part 1:

Demographic and clinical characteristics of patients

We included 140 patients who presented in AF to the electrophysiology laboratory for 153 pulmonary vein isolation procedures. The mean age was 62.1±9.2 years, 71% were male, and 67.1% of patients had persistent or longstanding persistent AF (Table 1).

Patient characteristics	Value (n, %)
Age	62.1±9.2 years
Male gender	100 (71.4%)
Persistent AF	94 (67.1%)
History of CHF	13 (8.5%)
Cardiomyopathy †	10 (6.5%)
Coronary artery disease	15 (9.8%)
Hypertension	85 (55.6%)
BMI	28.2 (21.2-35.1)
Prior surgical ablation	2 (1.3%)

Table 1. Demographic and clinical characteristics of patients
† Hypertrophic, dilated or post-infarction with ejection fraction<50%

Surface ECG measurements

Table 2 summarizes the values of DF and OI measured on the surface ECG after QRST subtraction among different leads according to the type of AF. On the surface ECG, DF was uniformly higher in persistent compared to paroxysmal AF, and OI was generally lower in persistent compared to paroxysmal AF.

Lead	DF	DF (Parox)	DF (Persist)	p	OI	OI (Parox)	OI (Persist)	p
V1	5.6±0.8	**5.3±0.7**	**5.8±0.8**	<0.01	0.39±0.1	0.38±0.1	0.40±0.1	0.20
V5/V6	5.5±0.8	5.2±0.7	5.6±0.9	0.08	0.30±0.1	0.31±0.1	0.29±0.1	0.18
aVL	5.37±0.8	**5.0±0.7**	**5.5±0.9**	<0.01	0.34±0.1	0.36±0.1	0.34±0.1	0.17
II/III/aVF	5.5±0.8	**5.2±0.8**	**5.6±0.9**	<0.01	0.36±0.1	**0.40±0.1**	**0.35±0.1**	<0.02

Table 2. Surface ECG Spectral Measures
Parox=paroxysmal atrial fibrillation. Persist = persistent atrial fibrillation

Intracardiac recordings

Table 3 shows DF and OI measurements for intracardiac recordings from different electrode bipoles according to the type of AF. Similar to surface ECG findings, DF was higher and OI lower in persistent AF compared to paroxysmal AF.

Recording site	DF	DF (Parox)	DF (Persist)	p	OI	OI (Parox)	OI (Persist)	p
CSd	5.55± 0.8	**5.1±0.7**	**5.8±0.8**	<0.01	0.35± 0.1	**0.38±0.1**	**0.33±0.1**	<0.01
CSp	5.33± 0.8	**5.0±0.8**	**5.5±0.8**	<0.01	0.35± 0.1	**0.38±0.1**	**0.34±0.1**	0.01
His	5.41± 0.8	**5.1±0.9**	**5.5±0.8**	0.03	0.29± 0.1	**0.32±0.1**	**0.28±0.1**	0.03
RA	5.48± 0.7	**5.1±0.6**	**5.7±0.6**	<0.01	0.4±0. 1	0.39±0.1	0.40±0.2	0.74

Table 3. Intracardiac electrogram Spectral Measures

Comparing surface ECG spectral indices with those of 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) (Figure 2).

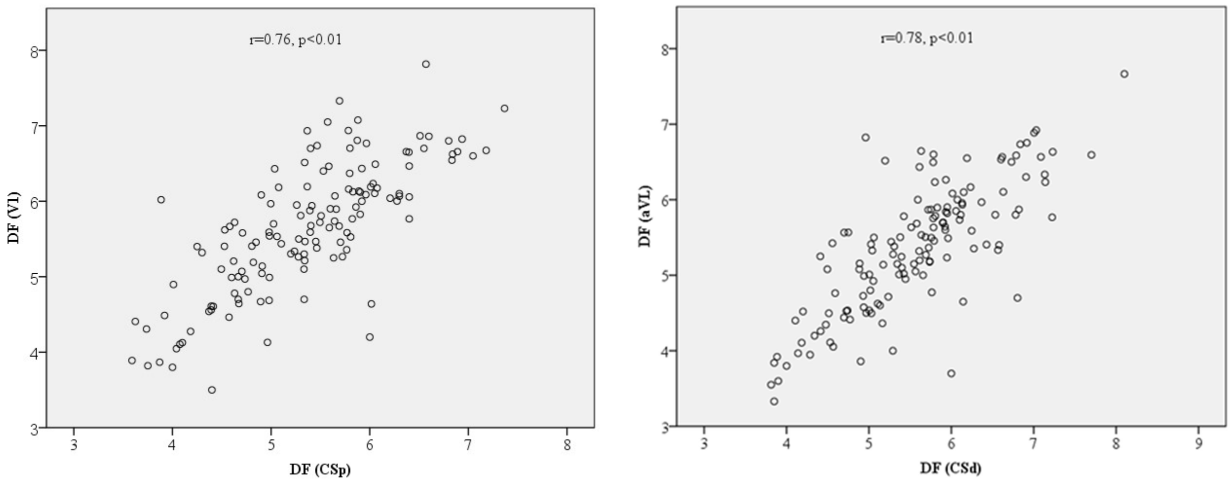


Figure 2. Correlation between DF values derived from intracardiac recordings and surface ECG (CSp and lead V1 and CSd and aVL, respectively)

For patients with paroxysmal AF, 66.7% had a positive left-to-right atrial DF gradient (CSd-RA= 0.048 (-0.07, 0.68)), whereas for persistent AF only 40% had a positive left-to-right atrial DF gradient (CSd-RA=-0.05 (-0.46, 0.25); (p=0.061) (Figure 3). Figure 4 demonstrates spectral analysis in a patient with a higher DF and lower OI in the RA compared to the CSd.

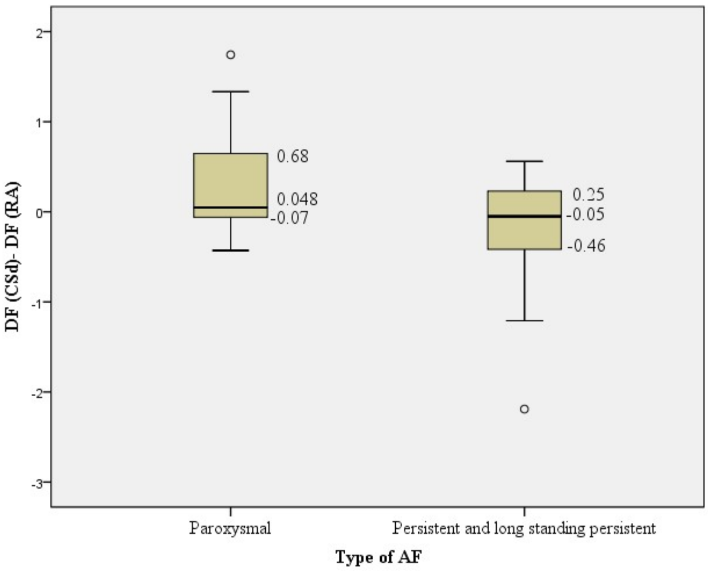


Figure 3. Left-to-right DF gradient in paroxysmal and persistent AF patients. Note the median positive gradient in paroxysmal patients but a negative median gradient in those with persistent and long-lasting persistent AF.

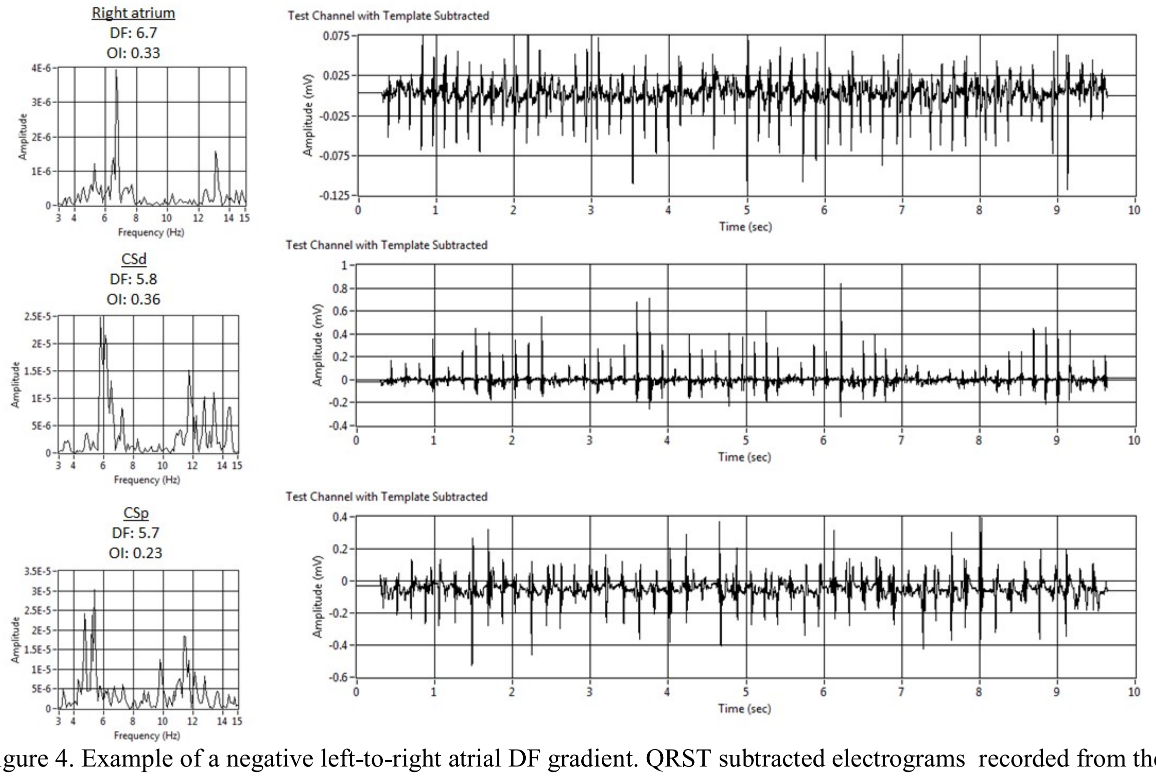


Figure 4. Example of a negative left-to-right atrial DF gradient. QRST subtracted electrograms recorded from the RA, CSd and CSp of a persistent AF patient showing faster right atrial activation corresponding to higher DF and lower organizational index compared to CSd and CSp locations.

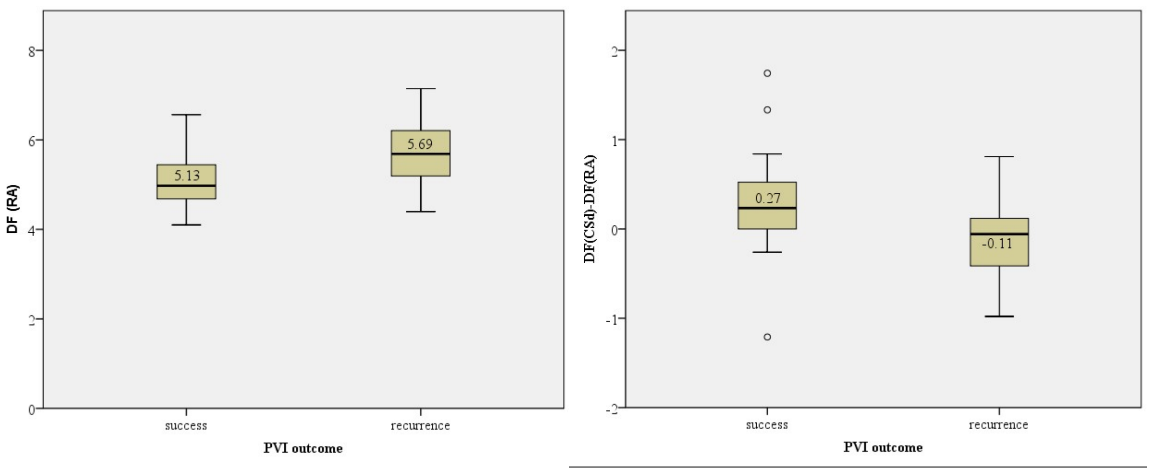
Prediction of AF recurrence after PVI

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

The following variables predicted recurrent AF after PVI on univariable analysis: higher DF in aVL (OR=1.69, 95% CI 1.11-2.56, p=0.014), higher DF in CSp (OR=1.58, 95% CI 1.03-2.44, p=0.035) and CSd (OR=1.68, 95% CI 1.1-2.55, p=0.014), lower OI in CSd (OR=0.012, 95% CI 0.0001-0.41, p=0.014), higher DF in RA (OR=4, 95% CI 1.38-11.51, p=0.011), lower CSd-to-RA DF gradient (OR=0.19, 95% CI 0.044-0.85, p=0.03) and lower OI in the inferior leads (OR=0.007, 95% CI 0.0001-0.23, p=0.006). 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.

In a multivariable model that included age, gender, BMI, type of AF, history of hypertension, coronary artery disease, cardiomyopathy, and prior congestive heart failure, only three variables predicted recurrent AF after ablation: higher DF in RA (OR=3.52 95% CI 1.18-10.46, p=0.023), lower CSd-to-RA DF gradient (OR=0.2, 95% CI 0.04-0.88, p=0.034), and lower OI in the inferior ECG leads (p=0.051). When examining clinical parameters alone, we found type of AF to be the strongest predictor of AF recurrence with an OR of 4 (95% CI 1.89-8.42, p=0.0001); however, this was not an independent predictor of AF recurrence when spectral parameters were included in the model. Quantitatively, the patients with recurrent AF compared to AF freedom after PVI had a higher DF in RA (5.7±0.68 vs 5.13±0.6, p=0.005), lower CSd-to-RA DF gradient (-0.2±0.58 vs. 0.27±0.63, p=0.007), and lower OI in the inferior ECG leads (0.35±0.1 vs. 0.4±0.1, p=0.008) (Figure 5). Higher DF in RA predicted unfavorable outcome with an area under the curve (AUC) of 0.73 (95% CI 0.59-0.88, p=0.007). An RA DF value of >5.07 predicted AF recurrence with a sensitivity of 82% and specificity of 61%, whereas a cutoff of 6.04 had a specificity of 94% and sensitivity of 43%. A lower CSd-to-RA gradient predicted AF recurrence with an AUC of 0.74 (95% CI 0.59-0.89, p=0.007) (Figure 6).

Patients with AF recurrence after PVI exhibited a higher DF in the right atrium, a negative left-to-right atrial DF gradient and lower organizational index in the inferior leads compared to those with a successful ablation.



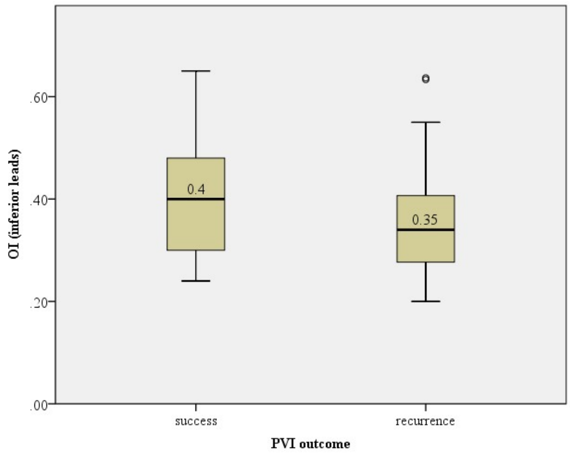


Figure 5. Parameters of the power spectrum according to the outcome of the PVI

A lower OI in the inferior leads predicted AF recurrence with an AUC of 0.63 (95% CI 0.53-0.72, p=0.008); OI values lower than 0.33 had a sensitivity of 31% and a specificity of 55% for predicting AF recurrence, whereas values lower than 0.22 had a specificity of 94%. The intraobserver reliability for visual classification of fibrillatory appearance as fine, coarse, or indeterminate for the 2 ECG segments was 93.3% for Observer 1, 97.3% for Observer 2 and 80.3% for Observer 3, while Kappa for interobserver reliability was 0.083 (95% CI -0.03-0.19, p=0.155). None of the observers could predict ablation success at 1 year (Observer 1: p=0.08, Observer 2: p=0.28, Observer 3: p=0.1), nor did the pooled evaluation of atrial activation between the three observers (agreement in 71/153 cases) (p=0.2).

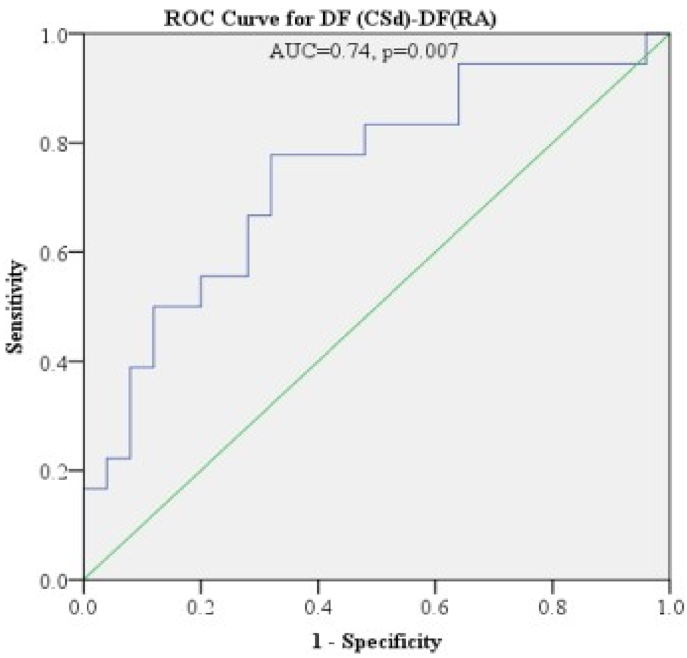


Figure 6. AUC curve for the left to right DF gradient as a predictor of successful ablation. A positive left to right gradient had a fair predictive value for PVI success. AUC = area under the curve ROC = receiver operating characteristic

Part 2:

Demographic and clinical characteristics of patients

One hundred fifty-two patients underwent repeat ablation for recurrent atrial arrhythmias after PVI from July 2011-July 2016. Of these, 25 patients (16.4%) had isolated PVs at the time of the procedure- 8.9% (9/101) of paroxysmal AF and 32.7% (16/48) of persistent AF patients. Table 4 summarizes the demographic and clinical characteristics of PVi and PVr patients. PVi patients were more likely to have persistent AF at the time of their first PVI (64% vs. 26%; p<0.0001), obesity (BMI 30.4 (27-33.9) vs. 28.2 (24.8-31.5), p=0.05) and a trend towards more prior ablations (1.4±0.7 vs. 1.2±0.4, p=0.093). Patients with PVi were also more likely to have had the prior ablation with a contact-force sensing catheter compared to the PVr group (7/25 (28%) vs 1/127 (0.8%); p<0.0001). All patients had previously undergone at least one wide area antral pulmonary vein isolation performed either at our institution or an outside hospital, either with radiofrequency ablation in 86%, cryoablation in 6%, or a surgical MAZE procedure in the remaining 8% of patients. In addition, a mitral line was delivered in 8 patients, cavotricuspid isthmus line in 40 patients, roof line in 14 patients, CFAE ablation in 6 patients, posterior wall isolation in 4 patients and SVC isolations in 5 patients during the prior procedure(s). Antiarrhythmic drugs (AADs) used by the patients prior to ablation (often > 1) included Propafenone (35.3%), Flecainide (40%), Dofetilide (30%), Dronedarone (14%), Sotalol (12.4%) and Amiodarone (22%), with no significant difference in AAD utilization between the groups.

	PVi n (%)	PVr n (%)	p
Number of patients	25 (16.4%)	127 (83.6%)	
Age (years)	63 (55.5-68)	63 (55.5-68)	0.94
Male gender	14 (56%)	87 (68%)	0.22
Persistent AF *	16 (64%)	33 (26%)	<0.0001
History of CHF †	0	9 (7%)	0.35
Hypertension	16 (64%)	68 (53.5%)	0.33
BMI (kg/m^2) ‡	30.4 (27-33.9)	28.2 (24.8-31.5)	0.05
Cardiomyopathy §	3 (12%)	11 (9%)	0.70
Coronary artery disease	2 (8%)	13 (10%)	1
Obstructive sleep apnea	5 (20%)	17 (13%)	0.36
Prior surgical ablation	4 (16%)	11 (8.7%)	0.27
Prior flutter ablation (typical+atypical)	8 (32%)	38 (30%)	0.83
Number of previous AF ablations	1.4±0.7	1.2±0.4	0.09
Contact force catheter at prior PVI	7 (28%)	1 (0.8%)	<0.0001

Table 4. Demographic and clinical characteristics of PVi and PVr patients
Values are n (%), mean±SD or median (interquartile range)
* Arrhythmia at the time of first ablation, † Clinical congestive heart failure, ‡ Body mass index
§ Hypertrophic, dilated or post-infarction with ejection fraction<50%

Procedural data

PVi patients

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) (Figure 7).

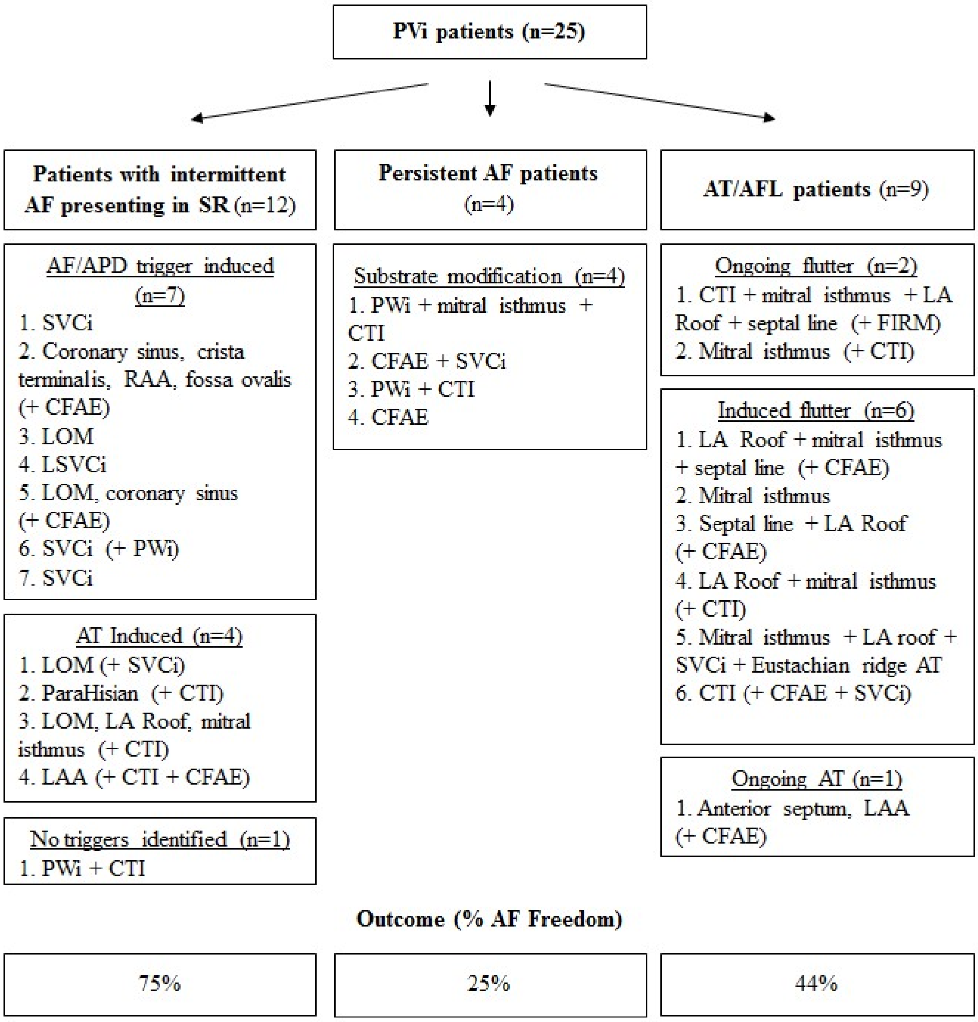


Figure 7. Ablation performed in each patient, classified by the dominant presenting arrhythmia in PVi patients. Outcome after ablation also presented in the bottom panel. CTI: cavotricuspid isthmus line, CFAE: Ablation of complex fractionated atrial electrograms, PWi: Posterior wall isolation, AT: atrial tachycardia, LOM: Focal ablation of the LOM region, RAA: right atrial appendage; SVCi: superior vena cava isolation, LSVCi: left superior vena cava isolation.

In patients with intermittent AF presenting in SR, triggers for AF or reproducible APDs were elicited from the following locations: the SVC (n=4), other right atrial sites such as the crista terminalis (n=1), fossa ovalis (n=1), para-Hisian region (n=1), base of right atrial appendage (n=1) and left atrial sites such as the left atrial appendage (LAA) ridge/ligament of Marshall (LOM) (n=4), the base of LAA (n=1) and CS (n=2) (Figure 8).

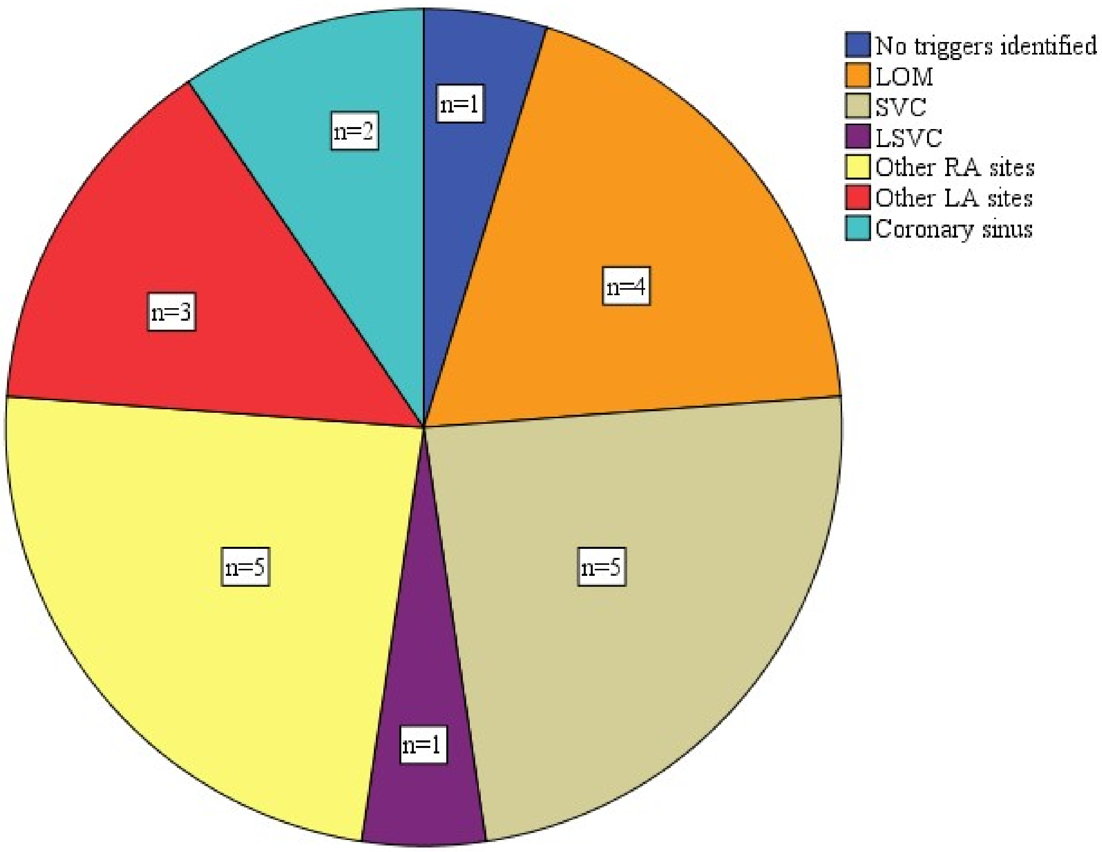


Figure 8. Source of triggers of AF/APDs elicited by isoproterenol in patients with isolated pulmonary veins.

One patient had a persistent left-sided superior vena cava (LSVC) and AF was induced from within this vein (Figure 9). Patients with SVC triggers all underwent SVC isolation, incomplete due to phrenic nerve proximity in one patient. In no cases was LAA isolation or complete CS isolation performed. In 8 patients, additional ablations were performed such as antral expansion of the ablation line (n=3), CFAE ablation (n=3), posterior wall isolation (n=1) as well as linear ablation: cavo-tricuspid isthmus (CTI) (n=3), roof line (n=1) and a posterolateral line to the mitral annulus (n=1). In one patient there were no inducible AF triggers or flutters; therefore, an empiric posterior wall isolation and CTI ablation was performed.

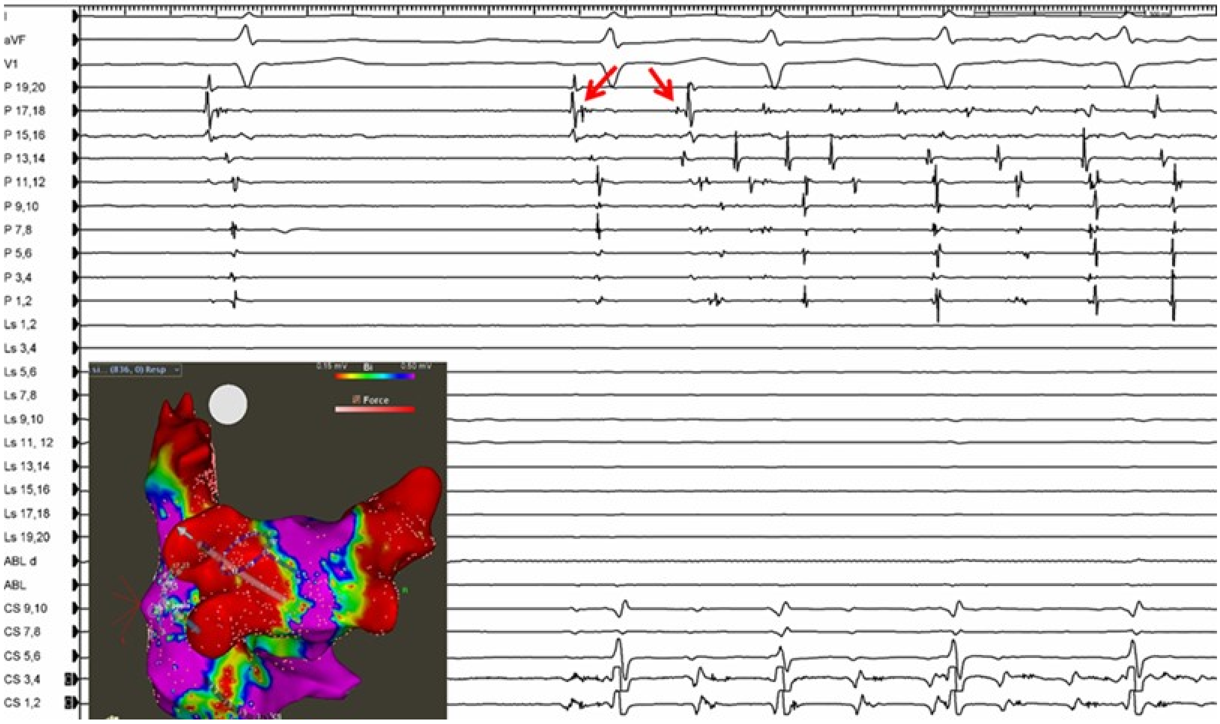


Figure 9. Intracardiac electrograms from a patient with persistent AF, isolated pulmonary veins and a persistent left superior vena cava. An electroanatomic voltage map is also shown; red represents electrical silence (voltage <0.1mV) and purple healthy myocardium (>0.5mV). A circular mapping catheter (Ls) is present in the left superior pulmonary vein and a multispline catheter (P) in the left SVC. After cardioversion, tracings showing 2 sinus beats followed by early recurrence of atrial fibrillation triggered from a left SVC potential (red arrow). There is electrical silence on the circular mapping catheter inside the left pulmonary veins. This patient was treated with SVC isolation and has had no further recurrences of AF. (CS=coronary sinus; Abl=ablation catheter).

In the 4 patients who presented to the lab with persistent AF, there were no triggers elicited after cardioversion with isoproteronol, and no flutters present at baseline or with burst pacing. The ablation strategy was empiric in these cases and included CFAE ablation (n=2), empiric SVC isolation (n=1), CTI line (n=1), posterior wall isolation (n=2) and the redo of previous surgical lines with gaps (n=1, anterolateral line to the mitral annulus and CTI line).

In 9 patients flutters or focal atrial tachycardias were present at baseline (n=3) or induced with isoproteronol or burst pacing (n=6). These included atrial tachycardias from the Eustachian ridge (n=2), from the base of the LAA (n=1) and the anterior septum (n=1), mitral annular flutter (n=5), LA roof-dependent flutters (n=2), CTI dependent flutter (n=4) and septal flutters (n= 4). Ablation targetted these flutters and included 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%).

Overall, in the pooled group of PVi and PVr patients, 5/14 roof lines were reablated; in 4/5 patients block was achieved across the line. Mitral lines were reablated in 3/8 patients with block achieved in all cases. There were 7/40 CTI lines requiring additional ablation to achieve bidirectional block, all of which were successful. One patient required reisolation of the SVC. The following new linear ablations were performed (total #/ bidirectional block rate): CTI lines (26/100%), roof lines (14/71%), mitral lines (16/56%).

Outcome

After 18.8±15 months, fewer PVi patients than PVr patients remained in sinus rhythm (56% vs. 76%; p=0.036). Patients with PVi also had earlier AF/AT recurrences (Log-rank, Breslow and Tarone-Ware tests p=0.0001) (Figure 10). More PVi patients remained on an AAD (60% vs. 30.7%, p=0.005). Antiarrhythmic drugs utilized overall after ablation included: 20% Dofetilide, 8.5% Flecainide, 7.2% Propafenone, 1.3% Sotalol and 4.6% Amiodarone. One patient from each group had an AV junction ablation and a biventricular pacemaker implantated due to recurrent, intractable AF or atypical flutters.

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%), occasional AF in one patient and 2 patients with recurrent AF. 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.

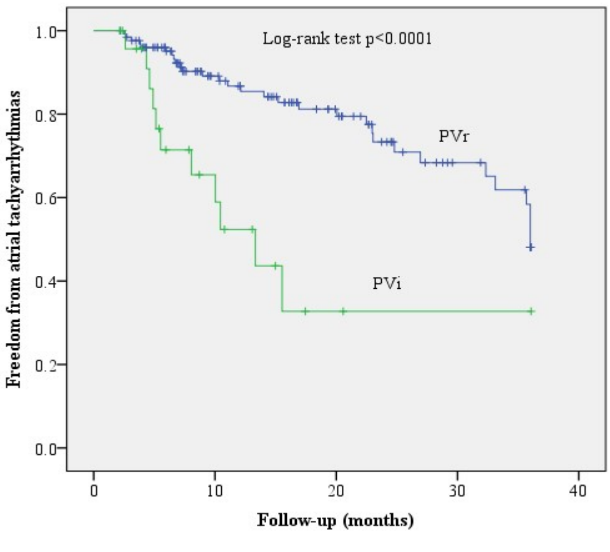


Figure 10: Kaplan-Meier survival curves for patients with isolated pulmonary veins (PVi) vs. those with pulmonary vein reconnections (PVr).

We also investigated the relationship between the number of reconnected veins and the outcome of redo ablation. Patients with PVi had a success rate of 56%, patients having 3 or 4 PV reconnections 70.1% and those with only one or two reconnections 90% (p=0.007); these groups also exhibited significantly different survival curves with Kaplan-Meier analysis (Log-Rank test p<0.0001) (Figure 11).

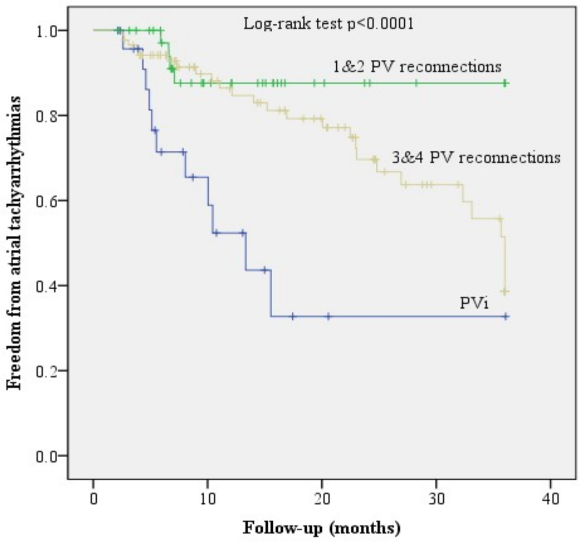


Figure 11. Kaplan-Meier survival curves for freedom from tachyarrhythmias after repeat ablation according to the number of pulmonary veins reconnected at the time of the redo ablation. PV=pulmonary vein.

On univariable analysis, PVi (HR=3.9, 95% CI 1.9-8.1, p=0.0001), history of cardiomyopathy (HR=4.91, 95% CI 1.9-12.3, p=0.001) and the presence of chronic lung disease (HR=6.8, 95% CI 1.53-29, p=0.011) were all predictors of AF recurrence. Persistent or longstanding persistent AF showed a trend towards worse outcome (HR=1.8, 95% CI 0.997-3.5, p=0.051). On multivariable analysis that included the presence of isolated veins at the time of the redo procedure, age, gender, BMI, type of AF, hypertension, coronary artery disease, prior clinical episode of congestive heart failure and cardiomyopathy, only PVi (HR=3.6, 95% CI 1.6-8.3, p=0.002) and history of cardiomyopathy (HR=6.2, 95% CI 2.3-16.3, p<0.0001) remained significant predictors of recurrent AF.

Discussion

Outlined above are two attempts to complement the empiric isolation of the pulmonary veins in terms of patient selection and ablation technique: spectral analysis of the fibrillatory activity of the atria during AF and the study of non-PV ablation targets in patients with recurrent AF despite isolated pulmonary veins.

As part of the first project we searched for surface ECG predictors of AF recurrence that could be used as simple, widely accessible tools for patient selection. However, only OI in the inferior leads had a predictive value close to significance, and its low specificity may not justify excluding patients from ablative therapy. The use of this measure requires prospective validation. Furthermore, prediction of PVI success based on the visual evaluation of the fibrillatory activity proved to be highly subjective and unreliable. Spectral measures derived from the intracardiac electrogram, namely higher RA dominant frequency, lower CSd to RA DF gradient had better predictive value for AF recurrence in this study and were significant despite the variability in AF substrate and ablation technique among the seven operators at UCSF.

Certainly, if pulmonary vein (PV) reconnection alone was the dominant cause of AF recurrence after ablation, one would not expect spectral analysis to have much predictive value. The fact that spectral analysis is useful suggests it is detecting structural remodeling that leads to a higher AF recurrence rate after ablation. Some patients with advanced remodeling may do poorly with PV ablation. Although MRI detection of fibrosis has been identified as one approach to risk stratification[19], this approach is costly and has not been uniformly reproduced. These spectral measures suggest a more remodeled atrial substrate and 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. Notably, spectral measures performed as well as AF type for predicting AF recurrence; this suggests that prior duration of AF may not be a sufficiently accurate marker of remodeling in all patients.

Overview of the literature

1. *Predictors of the outcome of pulmonary vein isolation based on the surface ECG*

Several studies focused on a non-invasive method for predicting catheter ablation outcome by analyzing the time and frequency domain of the atrial activation during atrial fibrillation. Matsuo et al. found that a longer atrial cycle length on the surface ECG was an independent predictor of success in persistent and longstanding persistent AF3. In a study published by Alcaraz et al. the analysis of the power spectrum of AF from the surface ECG did not reveal a single parameter that predicted the long-term outcome of atrial fibrillation ablation; however, 3-item logistic models for paroxysmal and persistent AF patients performed well. More specifically, a more organized AF predited long-term maintenance of sinus rhythm[20]. Our results corroborate these findings, as a higher OI in our analysis predicted better outcome. Lankveld et al. investigated a series of clinical and surface ECG-related parameters to predict the acute termination of AF during the electrophysiologic study as well as the long-term outcome of the catheter ablation and found several univariate predictors. As in our study, a lower DF and a higher OI were predictors of favorable outcome; the importance of the fibrillatory wave amplitude was also stressed. The combination of all of these ECG and clinical variables yielded an AUC of 0.71±0.12 for prediction of long-term outcome of catheter ablation[21].

2. *High DF in the RA as a predictor of unfavorable outcome of PVI*

The pulmonary veins and the left atrium are considered the principal initiators and perpetuators of AF, so pulmonary vein isolation has become the standard of care. In paroxysmal AF patients, a frequency gradient has been described between the atria, with the highest frequencies demonstrated at the PV-LA junctions, lower frequencies in the coronary sinus (CS), and lowest in the RA posterior wall[22], and this gradient can be abolished by PV isolation[23]. However, some studies found that in a minority of patients, non-PV DF locations such as the right atrium can drive atrial fibrillation. While there was a PV/posterior left atrial wall DF predominance in paroxysmal patients, Sanders et al. demonstrated a right atrial predominance in about one-third of paroxysmal and persistent patients[24], and Atienza et al. showed an increase in the prevalence of right atrial locations for maximum DF (DF max) from 4% in paroxysmal AF patients to 16%

in persistent AF patients. Atienza et al. also reported that patients who had DFmax sites left untargeted had a worse outcome after ablation[25]. Hasabe et al. demonstrated that AF initiated by RA triggers had the highest DF in the RA with a gradient towards the LA, which was augmented by adenosine triphosphate (ATP) administration[26]. Hocini et al. found that after LA ablation, 19% of patients had a right to left atrial frequency gradient, and additional RA ablation terminated AF in 55% of patients. This group had a longer history of atrial fibrillation and larger right atrium. During a mid-term follow-up, 88% of patients in whom right atrial ablation terminated AF at the index procedure were free from AF[27]. In our study, we found that the CSd-to-RA DF gradient predicted favorable outcome after ablation, with the majority of patients with recurrent AF having a negative CSd-to-RA gradient. Based on pre-ablation spectral analysis, it might be hypothesized that this latter group of patients may have benefited from RA ablation.

We concluded that a higher RA dominant frequency, lower CSd-to-RA DF gradient, and lower organizational index of the inferior surface ECG leads predicted recurrent AF after PVI. An RA dominant frequency >6 was highly specific for recurrent AF after catheter ablation. The above mentioned findings were independent of the type or duration of AF. These spectral measures suggest a more remodeled atrial substrate and may provide a simple tool for risk stratification or guidance towards additional non-PV substrate modification in patients referred for AF ablation.

<u>In the second study</u> we described the challenges of AF ablation in patients with isolated PVs. We found that 16% of patients returning to our electrophysiology laboratory for redo AF ablation had persistent isolation of all PVs. The ablation strategy in these patients consisted primarily of targeting non-PV triggers and atypical flutters in addition to other substrate modification. In this challenging group, 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.

In the past, recurrence after AF ablation was always due to the high incidence of PV reconnection. We found that prior use of contact force catheters was much more common in the PVi group, and likely accounts for much of the improvement in persistent PV isolation. As this population grows, it is important for electrophysiologists to have a clear ablation strategy and understand the limitations of repeat ablations in patients with isolated PVs. It is also important to give patients appropriate expectations, including the need to remain on an antiarrhythmic agent in many cases. Finally, there is a growing body of evidence emphasizing the importance of risk factor modification (weight loss, sleep apnea treatment, glycemic control, etc) in improving the outcome of AF ablation[28]. This should certainly be emphasized in hopes it may reduce the later recurrence of new non-PV triggers. The approach to ablation in patients with isolated PVs and no inducible AF triggers or flutters remains challenging. Variable approaches were used in our experience including antral extension of PVI lesions, box isolation of the posterior wall, CFAE ablation, and in some cases empiric isolation of common non-PV trigger sites. It is interesting, though, that in 8 of the 12 patients who presented in sinus rhythm with paroxysmal AF and PVAi, triggers were found in the SVC and/or the anterior ridge along the left PVs/left atrial appendage. Isolation of the SVC and ablation of the LSPV/LAA ridge would therefore be reasonable if no non-PV triggers or flutters can be elicited.

Prior work

Prior studies of redo pulmonary vein isolations reported that 4-41% of patients had persistent PV isolation [29,30,31,32,33,34]. The enrollment period of these studies preceded the routine use of contact force-sensing catheters reported their use at the time of the PVIs preceding the index procedure. The higher proportion of patients with isolated veins in our study population might be due to the introduction of their use into our practice.

Kim et al. and Sadek et al. described ablation strategies for PVi patients that incorporated trigger induction, linear ablation as well as CFAE ablation. Sadek et al. found that a strategy to aggressively target AF/AT triggers or empirically ablate common trigger sites resulted in success in 65% of patients[27]. Our data support those findings as 72% of patients in the intermittent AF group where a trigger could be elicited had favorable outcome. Baldinger et al. concluded that patients presenting for repeat ablation with regular tachyarrhythmias had the best outcome[31]. The only other study to compare the outcome of patients with persistent PV isolation to those with reconnected PVs was published by Kim et al. who demonstrated worse outcome for PVi patients[30].

Limitations for 2nd study

This is a single-center retrospective study of a relatively small population of patients with recurrent AF despite persistent PV isolation; the conclusions formulated here need prospective validation. The first PVIs were done by a variety of operators as in most centers performing PVI, which supports the real world experience of the results. Some of the previous procedures were not performed at UCSF and might have been performed with a different technique. Left atrial appendage isolation has been reported to reduce AF recurrences in persistent AF patients[3536]; however this has also been associated with left atrial thrombus and was not performed at UCSF.

To summarize, patients with recurrent AF and isolated pulmonary veins have a more advanced AF substrate and are more likely to have recurrent atrial tachyarrhythmias after redo ablation compared to patients with pulmonary vein reconnections. Nevertheless, a strategy of targeting non-PV triggers and inducible flutters can still lead to AF freedom in more than half of the patients during medium term follow-up. An understanding of the approach to ablation and outcome after ablation in this challenging group of patients is important for patients and cardiologists.

II. Comorbidities and Markers of Disease Progression Predict Catheter Ablation Outcome

There is considerable data available about the predictors of ablation success in atrial fibrillation that might aid patient selection and ablation strategy (Table 1). Table 2 shows patient characteristics associated with the good ablation outcome.

1. Lone AF

The apparent lack of predisposing factors is illustrated by an old concept that describes atrial fibrillation without underlying heart disease or traditional risk factors– lone atrial fibrillation[37]. It has been used in a variety of ways in the literature leading to confusion, but essentially it refers to patients <60 years old without significant coronary artery disease or diabetes who have normal echocardiography, thyroid function tests and in whom concurrent infection could be excluded[38]. Currently the concept is being challenged as our investigative repertoire to pick up clinical and genetic predisposing factors has improved greatly and groups are advocating for avoidance of the term altogether[39].

2. Predictors of AF ablation outcome

It is a well-known fact that a more extensive atrial remodeling indicates worse outcome. Known clinical factors influencing atrial remodeling include type of AF[40], longer duration of AF[41], valvular heart disease[42], cardiomyopathy[43], sleep apnea (OSA)[44], diabetes[45], obesity[46], uncontrolled hypertension[47], etc. Surrogate markers of remodeling that predict ablation outcome have been identified as well, such as a more advanced atrial fibrosis on LGE MRI[48] or more extensive low voltage zones (<0.5 mV) with voltage mapping[49], greater LA volume[50,51] or diameters[52], left atrial asymmetry as evidenced by CT angio in persistent AF patients[53], LA appendage structural remodeling[54], impaired adaptation to pressure of the LA[55], higher DF of drivers maintaining AF[56], etc.

3. Duration of AF

The AFA long term registry revealed the real-life situation of AF ablation across Europe with a subanalysis showing that an AF history longer than 2 years resulted in a significantly lower success rate. Although patients with longer duration of AF were older and had more comorbidities such as ischemic heart disease, hypertension, duration of AF was an independent predictor of AF recurrence[57]. These findings were corroborated by Hussein and colleagues who found that performing catheter ablation after a 3-year history of persistent AF resulted in worse outcome with multivariable analysis, as was a significantly higher BNP and CRP value and a larger LA diameter, known markers of inflammation and cardiac strain[58]. It is worthwhile remembering however that the history of AF may not correlate well with the duration of AF episodes and the extent of atrial remodeling.

4. Obstructive sleep apnea

Linz et al demonstrated a significantly higher prevalence of OSA in AF patients vs. general population (21% to 74% vs. 3% to 49%)[59]. OSA creates episodes of hypoxemia and negative tracheal pressure that by means of vagal activation shortens the atrial ERP and increases atrial fibrillation inducibility from 0% at baseline to 90%[60]. OSA related changes to the atrial substrate include lower atrial voltage amplitude, slower conduction velocities, a more extensive electrogram fractionation as well as a higher incidence of extraPV triggers[61] contributing to poorer prognosis of catheter ablation[62],[63].

5. Alcohol consumption

Alcohol consumption is a risk factor that has been shown to alter ionic currents[64], cause oxidative stress[65] and modify cellular metabolism[66] among other effects. Regular moderate alcohol consumption is associated with lower LA conduction velocity and higher degree of atrial fibrosis[67]. Furthermore, this modifiable risk factor for AF can have an impact on catheter ablation outcome. Qiao et al reported an increase in AF recurrence with a HR of 1.579 in a population of paroxysmal AF patients, an effect at least party mediated by more extensive left atrial low voltage zones[68].

Patient related variables	**Disease related variables**	**Procedure related variables**
Age[69]	Persistent AF[56]	High frequency jet ventillation[70]
Valvular heart disease[42]	Duration of AF[41]	Ablation index guided ablation[71]
Hypertension[47]	Extent of low voltage zones[91]	Ablation of triggers ellicited with Isoproterenol/Adenosine[72]
OSA[62,63]	Scar on LGE MRI[92]	Failure to terminate AF during ablation[73]
Obesity[46]	Left atrial appendage asymmetry[54]	Number of procedures[74]
Insulin resistance and diabetes[82],[45]	LA stiffness[99]	Confirmation of entry and exit block[75]
Metabolic syndrome[76]	LA strain[98]	Recurrence in the blanking period[79]
LV dysfunction[43]	LA antero-posterior diameter[90]	
Ischemic heart disease[77]	LA volume [78,50,51]	
Alcohol consumption[68]	PR prolongation[116]	
Smoking[79]	P wave duration[117]	
Clinical scores[87,88,89]	Cycle length of AF[118]	
	Dominant frequency of AF[56]	
	Extent of areas with CFAE[124]	

Table 1. Predictors of the outcome of AF ablation

6. Obesity

The effects of obesity have been demonstrated in an animal study published by Meng et al showing that a chronic high-fat diet induces a widening of the atrial interstitial space accompanied by myocyte disarray and downregulation of expression and altered distribution of gap junction proteins connexin 40 and connexin 43. These changes were in conjuncture with an increase in parameters traditionally associated with fibrosis, namely TGF-β1 and MMP-2[80]. Okumura et al showed that in pigs a high fat diet resulted in changes in the electrophysiological characteristics of the atria such as the shortening of ERP in the pulmonary veins and the superior vena cava (SVC) and an increase in the inducibility and duration of AF[81]. A 2013 meta-analysis confirmed worse catheter ablation outcome in high BMI patients, however not on multivariate analysis as comorbidities contributed to the effect. Nevertheless the authors noted a significant improvement in quality of life in these patients, albeit not due to lesser AF recurrence[46].

7. Insulin resistance

Hijioka et al revealed the role of insulin resistance in the pathogenesis of AF using HOMA-IR (homeostasis model assessment of insulin resistance), a value of ≧ 2.5 independenty predicting ablation failure with a HR of 1.287. Of note, patients with insulin resistance did not have a higher left atrial volume index (LAVI) or elevated inflammatory cytokines, such as TNF-α or TGF-β1 levels, yet they exhibited a significantly lower conduction velocity suggesting an effect on the electrophysiological, rather than structural properties of the atria. Patients enrolled in this study had paroxysmal AF and did not have scar areas on voltage maps[82]. Animal studies confirm that insulin resistance has an impact on AF inducibility[83] and genetically modified type II diabetes rats were shown to have a significantly greater number of repetitive atrial responses as well as longer intra-atrial activation times, but no differences in atrial refractoriness with EP testing[84]. Furthermore, Gu et al demonstrated that thiazolidinediones (peroxisome proliferator-activated receptor (PPAR)-γ agonists), due to their effect on growth factor release, cell proliferation and migration as well as extracellular matrix remodeling[85] were indepent predictors of AF free survival at 12 months (OR= 0.319)[86].

8. Clinical scores for prediction of AF ablation outcome

Several scores for predicting AF ablation outcome have been published incorporating known risk factors for AF progression and atrial remodeling. LAGO (AF phenotype, structural heart disease, CHA2DS2-VASc ≤ 1, LA diameter and LA sphericity) predicted poor ablation outcome with HR of 3.10 at 3 years[87]. In a study published by Potpara et al, the MB-LATER score (1 point for male gender, bundle branch block, left atrial diameter ≥47 mm, persistent AF and early recurrence of AF during blanking, 2 points for pre-ablation history of long-standing persistent AF) significantly predicted late recurrence of AF, however its predictive accuracy was poor (AUC 0.62) and none of the other tested predictive scores (CAAP-AF, CHA2DS2-VASc and CHADS2) yielded better results in this patient population[88]. In contrast, in a population of paroxysmal AF patients, Chao et al demonstrated that the CHADS2 score along with left atrial diameter were significant predictors of recurrent AF and identified patients with low (2.9%, with CHADS2 0 score) and high recurrence rates (63.6% with CHADS2 score ≥3) at 2 years[89].

9. Echocardiography parameters

Information about left atrial structural changes can be gained non-invasively and at low cost with echocardiography. Motoc et al evaluated LA antero-posterior diameter (LAD), LA minimum volume (LAmin) in paroxysmal patients and found that cut offs of 41 mm and 23.69 mL, respectively had a fair predictive value for recurrence of AF after catheter ablation (negative predictive values of 73% and 87.3%). Interestingly 30% of patients with recurrence had a LAD within normal range, however they exhibited remodeling in the infero-posterior axis (longitudinal remodeling)[90].

10. Atrial scarring

There is consensus regarding the fact that extensive low voltage areas (LVA) (<0.5 mV) are associated with poorer ablation success[91]. Scar tissue can also be quantified using MRI, a non-invasive and well studied imaging modality. Chelu and collegues published a study in which LGE MRI was performed in patients ablated for AF (which included a posterior wall debulking in 90% of patients) and showed that during a 5-year follow-up the degree of atrial fibrosis (Utah stage IV versus stage I), was independently associated with arrhythmia recurrence with a HR of 2.73. All patients with Utah stage IV atrial fibrosis experienced recurrent AF after ablation at 5 years[92]. Whether or not performing substrate modification in addition to PVI will improve outcome is a subject of debate. The STAR-AF trial conducted by Verma et al did not show any benefit if linear ablation or ablation of complex fractionated electrograms (CFAE) was performed in addition to pulmonary-vein isolation[93], however several authors reported a higher freedom from AF[94,95] including a 2017 meta-analysis[96].

11. Remodeling of the left appendage

Suksaranjit and colleagues described a similar impact of left atrial appendage structural remodeling (demonstrated by LGE on MRI) on the success of catheter ablation, patients in the highest tier or LAA fibrosis experiencing 73.3% AF recurrence versus 37.5% in patients in the lowest tier[54]. Although empirical isolation of the left atrial appendage would seem to be an obvious resolve, it has been shown to predispose to thrombus formation and stroke[97].

12. Left atrial function and stiffness index

Left atrial function can be assessed by measuring LA systolic strain which has been shown to be reduced in patients with AF and especially in those with AF recurrences after catheter ablation. Yasuda et al compared left atrial global strain, LA lateral total strain as well as LAVImax in patients with and without recurrence and found that LA lateral strain to be a significant predictor or AF recurrence with an AUC 0.84, outperforming LAVImax (having an AUC of 0.74 and unable to predict unfavorable outcome if the patient was in sinus rhythm during the echocardiographic measurements)[98].

Khurram et al introduced the term stiffness index (SI) to describe the impaired adaptation of the left atrium to changes in loading conditions. It is defined as the ratio of the change in left atrial pressure to the change in left atrial volume during the passive filling of the LA. The index was higher in persistent AF, older age, in patients with previous ablation(s) and in patients with AF recurrences after catheter ablation, with a recurrence rate of 5% in the lower quartile compared to 59% in the highest quartile[99].

Characteristic	**Value/Comment**
Age[69]	<65 years
Gender[100]	Male
Paroxysmal AF[40]	HR 3.32 for freedom from arrhythmia after repeat ablation(s)
Duration of persistent AF <6 months[101]	
Absence of comorbidities and structural heart disease – lone AF[79,102]	Success rate after repeat AF ablation(s) as high as 96%[79]
Physical fitness[103]	High cardiorespiratory fitness (>100% predicted METs on treadmill testing)

Weight loss[104]	≥ 10% loss conveys a 6-fold increase of probability of freedom from arrhythmia
Good glycemic control[105]	HbA1c <7% or improvement in HbA1c by >10% during the 1-year preceding ablation
Risk factor management (RFM)[106]*	HR 4.8 for freedom from arrhythmia
CPAP treatment in OSA[107]	Risk of AF recurrence similar to non-OSA patients
LA diameter	<43 mm[108], <41 mm[90]
Left atrial appendage (LAA) flow velocity[109]	>47.7 cm/s
LAVI[52,110]	<34.4 mL/m2
LA volume (CT measurement)[111]	<106 mL
LGE extent	<30% [112], <35%[113]

* RFM included good blood pressure control, weight and lipid management, glycemic control, sleep-disordered breathing management, smoking cessation and reduction of alcohol intake to ≤30 g/week

Table 2. Patient characteristics associated with the best AF ablation outcome

13. Predictors derived from the surface ECG

The surface ECG in sinus rhythm can be revealing as well; PR prolongation, a mark of atrial and atrioventricular conduction slowing has been shown to predict the development of AF[114] and was associated with the presence of left atrial low voltage areas[115], older age, the persistent form of AF, larger LA dimensions and higher LAVI. It was also a significant predictor of the outcome of catheter ablation (HR=1.969, 95% CI 1.343 to 2.886, P=0.001)[116]. These results were reiterated by Hu et al who measured P wave duration (PWD) and the difference between pre- and postprocedural values (PWD variation). They found that AF ablation shortened PWD in the inferior leads, V1 and a lesser shortening was associated with an unfavorable AF ablation outcome (PWD variation ≥-2.21 ms in lead II had a sensitivity and specificity of 85.29% and 83.94%, respectively; AUC of 0.868)[117].

14. Characteristics of fibrillatory activity

There are insights to be gained from the characterization of the fibrillatory activity during AF either based on the surface ECG or intracardiac electrograms that might indicate the complexity of the atrial substrate and the prospective outcome of AF ablation. Predictors of the success of catheter ablation can be derived from the time- and frequency domain of fibrillatory activity of the atria indicative of electrical remodeling, high dominant frequency (DF) sites representing either focal sources or reentries. A shorter cycle length[118], a higher dominant frequency and a decreased level of organization of AF[119,56,120] were shown to predict poor outcome. A lower ablation success was noted in patients with higher RA dominant frequency and lower CSd to RA DF gradient indicating the presence of a RA source not targeted by PV isolation and LA ablation[56]. Of note, no preprocedural surface ECG spectral parameter has been found that is easy-to-use and could reliably guide patient selection.

Do CFAEs arise at driver sites or are they merely the result of wave front collision and if so, what is the value of their ablation? Some argue they are pivot points, areas of local reentry and slow conduction and are responsible for the maintenance of AF[121],[122]. It is known that the % area of CFAE is larger and the mean CL of the CFAE is shorter in patients with a more remodeled LA[123]. The STAR-AF II and CHASE-AF trials did not demonstrate any added benefit to PVI with CFAE ablation[93],[124] and a recent metaanalysis showed that performing additional CFAE ablation increased ablation success only in persistent AF patients, albeit with a rise in procedure time, fluoroscopy time as well as postprocedural ATs[125].

15. Reverse remodeling

There is evidence suggesting reversal of remodeling after catheter ablation. Fujimoto found that a decrease in P-wave dispersion, a marker of prolonged and inhomogeneous impulse conduction starting from 3 months postablation indicates favorable outcome and reverse remodeling along with the decrease of left atrial size and BNP level. They also noted that the latency of the decrease suggests that the maintenance of sinus rhythm might be largely responsible for it[126]. A subgroup analysis of the CAMERA-MRI study showed a significant increase in the RA myocardial voltage especially at the posterior and septal segments as well as a significant decrease in complex fractionated electrograms besides improvements in LV function and LA area in heart failure patients who remained in SR >90% of time after catheter ablation[127]. In an elegant study, however Teh et al demonstrated further progression in terms of decrease in bipolar voltage, lengthening of the ERP, slowing of the conduction velocity as well as an increase in the proportion of complex signals despite a significant decrease in left atrial size. Interestingly, despite no AF reported during the follow-up, AF was inducible in the EP lab in 5/11 patients, three requiring cardioversion for AF lasting >60 minutes[128].

Conclusion

There is excellent basic science available on the pathophysiology of AF including changes in molecular biology, histology, ionic channel remodeling as well as computational models that demonstrate the arrhythmogenicity of fibrosis. Understanding the mechanism of AF initiation and maintenance and understanding the profound and multifaceted effect risk factors have on the structure and function of the atrial myocardium is key in developing more effective treatments.

There are many compelling investigative and therapeutic areas of research in atrial fibrillation ablation worth exploring that extend beyond the current mainstream therapy, the empiric isolation of the pulmonary veins. When considering a patient for AF ablation, one should look at all the available data to help the patient make an informed decision as well as give perspective regarding their disease. Apart from perfecting the technique of antral isolation of the pulmonary veins, advances in mapping and targetting additional triggers will likely hold the key to further improving long-term ablation success.

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